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ORIGINAL REPORT

Hydrocortisone as an Intervention for Dexamethasone-Induced Adverse Effects in Pediatric Patients With Acute Lymphoblastic Leukemia: Results of a Double-Blind, Randomized Controlled Trial

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A B S T R A C T

Purpose
Dexamethasone is a key component in the treatment of pediatric acute lymphoblastic leukemia (ALL), but can induce serious adverse effects. Recent studies have led to the hypothesis that neuropsychological adverse effects may be a result of cortisol depletion of the cerebral mineralocorticoid receptors. We examined whether including a physiologic dose of hydrocortisone in dexamethasone treatment can reduce neuropsychologic and metabolic adverse effects in children with ALL.

Patients and Methods
We performed a multicenter, double-blind, randomized controlled trial with a crossover design. Of 116 potentially eligible patients (age 3 to 16 years), 50 were enrolled and were treated with two consecutive courses of dexamethasone in accordance with Dutch Childhood Oncology Group ALL protocols. Patients were randomly assigned to receive either hydrocortisone or placebo in a circadian rhythm (10 mg/m^2/d) during both dexamethasone courses. Primary outcome measure was parent-reported Strength and Difficulties Questionnaire in Dutch, which assesses psychosocial problems. Other end points included questionnaires, neuropsychological tests, and metabolic parameters.

Results
Of 48 patients who completed both courses, hydrocortisone had no significant effect on outcome; however, a more detailed analysis revealed that in 16 patients who developed clinically relevant psychosocial adverse effects, addition of hydrocortisone substantially reduced their Strength and Difficulties Questionnaire in Dutch scores in the following domains: total difficulties, emotional symptoms, conduct problems, and impact of difficulties. Moreover, in nine patients who developed clinically relevant, sleep-related difficulties, addition of hydrocortisone reduced total sleeping problems and disorders of initiating and maintaining sleep. In contrast, hydrocortisone had no effect on metabolic parameters.

Conclusion
Our results suggest that adding a physiologic dose of hydrocortisone to dexamethasone treatment can reduce the occurrence of serious neuropsychological adverse effects and sleep-related difficulties in pediatric patients with ALL.

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INTRODUCTION

Dexamethasone has high antileukemic activity and excellent penetration into the CNS; thus, dexamethasone is commonly included in the treatment of pediatric acute lymphoblastic leukemia (ALL).[1-4] Unfortunately, however, dexamethasone treatment can cause robust neuropsychological and metabolic adverse effects. The reported frequency of patients who develop dexamethasone-related adverse effects that encompass mood, behavior, cognition, and sleep ranges from 5% to 75%.[5-10] Of importance, patients and their families report that these adverse effects are most detrimental with respect to quality of life.[5-10] Because many current ALL treatment protocols call for pediatric patients with ALL to receive pulses of dexamethasone for approximately 1.5 years, these adverse effects can have a major impact on the daily activities and development of the child.[5,9,11] To date, only one intervention study has been performed to investigate glucocorticoid-induced neuropsychological adverse effects. This study found that chlorpromazine and lorazepam reduced glucocorticoid-related symptoms[12]; however, because these agents can induce other adverse effects, including drowsiness, orthostatic hypotension, and paradoxical agitation, they should therefore only be prescribed for severe behavioral problems and/or psychosis.

Until recently, the pathophysiology of dexamethasone-related neuropsychological adverse effects was poorly understood.[7] For example, excessive activation of cerebral glucocorticoid receptors (GRs) by corticosteroid binding has been suggested to underlie neuropsychological adverse effects[7]; however, recent data have revealed that mineralocorticoid receptors (MRs) in the brain may play an even more important role in the regulation of mood, behavior, cognition, and sleep.[13,14] In the human brain, GRs and MRs have similar expression patterns; however, these two receptor types have strikingly different ligand affinities.[15] For example, dexamethasone has a 30- to 40-fold higher affinity for the GR than cortisol, whereas dexamethasone does not bind to the MR. In contrast, prednisolone binds the GR, but has a low affinity for the MR.[16] Finally, cortisol, that is, hydrocortisone, can bind both receptor types but has a higher affinity for the MR.[17] Both dexamethasone and prednisolone suppress production of cortisol via a negative feedback loop that acts on the hypothalamus-pituitary-adrenal axis[16]; however, prednisolone, but not dexamethasone, can bind and activate the MR. Thus, patients who are treated with dexamethasone have fewer cortisol-bound MRs, which may lead to more adverse effects.[18] Data from animal studies and small case series suggest that the resulting dexamethasone-induced cortisol depletion of MRs in the brain causes or exacerbates the adverse effects with respect to mood, behavior, and/or cognition.[13,14,19,20]

These key findings have led us to hypothesize that dexamethasone-induced cortisol depletion of the MR may underlie the neuropsychological adverse effects in pediatric patients with ALL.[21] Therefore, we examined whether these adverse effects can be reduced by adding physiologic dosages of hydrocortisone to dexamethasone treatment.[21] Of importance, we previously reported that hydrocortisone does not reduce dexamethasone sensitivity of the cells of patients with ALL ex vivo[21]; therefore, we performed a randomized controlled trial to determine whether including hydrocortisone in dexamethasone treatment regimen reduces the neuropsychological, metabolic, and physical adverse effects in children with ALL.

PATIENTS AND METHODS

Study Design and Participants

We performed a randomized, placebo-controlled, double-blind trial with a crossover design (Fig 1). The primary objective of our study was the reduction of psychosocial problems during dexamethasone treatment. The secondary objective was to study the influence of the addition of hydrocortisone during dexamethasone treatment on sleep-related difficulties, eating behavior, physical activity, cognitive functions, and metabolic parameters. Patients were recruited at five Dutch pediatric oncology departments. Patients with ALL (age 3 to 16 years) who were treated according to Dutch Childhood Oncology Group ALL-10 or ALL-11 medium-risk protocols, including dexamethasone pulses during the maintenance phase (after asparaginase and anthracyclines were discontinued), were eligible for inclusion. The following exclusion criteria were applied: a significant language barrier, evidence of preexisting intellectual disability, and any condition that could have interfered with the administration and/or absorption of the study medication and/or dexamethasone. Parents and legal guardians of patients provided written informed consent, and patients age 12 to 16 years also provided their own written informed consent.

The part of the maintenance phase during which intervention was conducted consisted of 19 consecutive treatment cycles that lasted 21 days each, in which patients received five consecutive days of dexamethasone treatment, vincristine once (first day of the cycle), 6-mercaptopurine once per day, and methotrexate once per week. The study included two 5-day courses of dexamethasone (6 mg/m^2/d, three doses containing 2 mg/m^2 each) with which each patient also received either placebo or hydrocortisone—in this crossover study, patients who were randomly assigned to receive hydrocortisone in the first course received placebo in the second course and vice versa (Fig 1). The median start of the study was in the fourth cycle after stopping asparaginase, and the median time between the two 5-day study courses was 3.0 weeks (interquartile range [IQR], 3.0 to 6.0) or one cycle. Daily dose of hydrocortisone was administered orally in three doses that contained 5, 3, and 2 mg/m^2 at the same time as dexamethasone and was designed to follow the normal circadian rhythm. Placebo was administered in a dose and scheme similar to those of hydrocortisone. A wash-out period of ≥ 16 days was included between dexamethasone treatment courses.

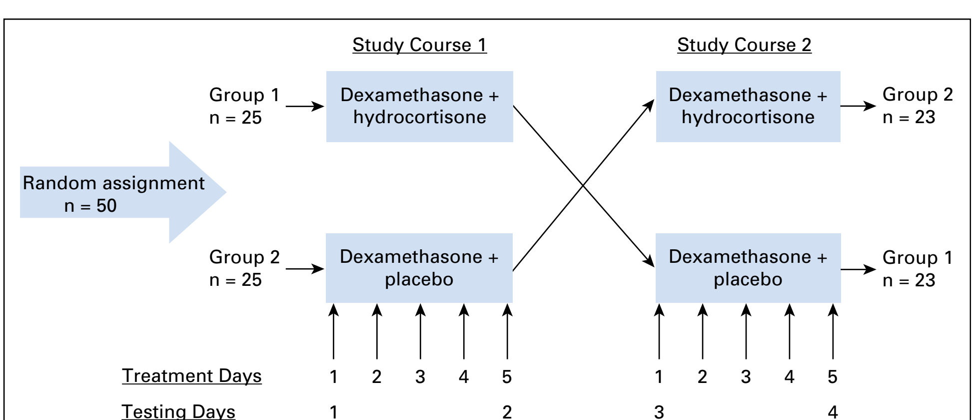

Fig 1. Study design.

Procedures

The primary end point was the total difficulties score from the parent-reported Strengths and Difficulties Questionnaire in Dutch (SDQ-Dut; Data Supplement). Secondary end points were obtained from additional questionnaires, neuropsychological tests (Data Supplement), and metabolic parameters. In each course, mood, behavior, cognition, and sleep were assessed on the morning of the first day of treatment, that is, before the start of dexamethasone treatment, and the morning of the fifth treatment day, that is, after a full 4 days of dexamethasone treatment.

Questionnaires. Parent-reported SDQ-Dut, which assesses psychosocial difficulties and strengths, has been validated in the Dutch population. The SDQ-Dut[22-25] is a brief questionnaire that assesses the psychosocial functioning of children and adolescents age 3 to 16 years by either parent reporting or self-reporting (for patients age 11 to 16 years). The questionnaire contains 25 items in the following five subscales (score ranges are in the Data Supplement): emotional symptoms, conduct problems, hyperactivity and inattention, peer relationship problems, and prosocial behavior. We calculated the total difficulties score, which is defined as the sum of the first four subscale scores, that is, excluding prosocial behavior. The impact of these difficulties on the life of the child was measured by using the impact of stress score. A higher SDQ total difficulties score reflects more problems. Ideally, both parents and all patients age ≥ 11 years completed the SDQ-Dut on all four testing days. On each testing day, participants were instructed to provide information regarding psychosocial problems experienced in the previous four days. SDQ-Dut scores obtained from the primary parent, defined as the parent who was present in the outpatient clinic at all four testing days, were used for all analyses. In the majority of cases, the primary parent was the mother of the patient.

The Sleep Disturbance Scale for Children (SDSC)[26] was used to assess sleep quality and sleep disturbances in patients. The SDSC has a combined score that covers the six most common sleep disorders experienced during childhood, which are disorders of initiating and maintaining sleep (DIMS), sleep breathing disorders, disorders of arousal, sleep-wake transition disorders (SWTDs), disorders of excessive somnolence (DES), and sleep hyperhidrosis. A higher score reflects the presence of more problems.

The Dutch Eating Behavior Questionnaire for children (DEBQ-C)[27] has three subscales: restrained eating, emotional eating, and external eating. A higher score on each subscale reflects the presence of more problems.

Daily physical activity was measured by using the Baecke Physical Activity Questionnaire (BPAQ),[28] which consists of 16 questions organized in three sections—school activity, sports activity, and leisure activity. With the BPAQ, a higher score on each scale reflects higher activity.

Neuropsychological assessment. Neuropsychological tests that were designed for children and young adults were used to assess skills in four domains: memory, attention, visual-spatial functions, and processing speed (Data Supplement). The neuropsychological tests were performed by the same investigator (L.T.W.) on all four testing days.

Physical parameters, anthropometric measurements, and laboratory tests. Parents and children were instructed to maintain a diary of the dietary activity of the child during the first four treatment days in each study course (Data Supplement). Height (meters), weight (kilograms), waist-hip circumference (centimeters), and blood pressure (millimeters of mercury) were measured on all four testing days.

Physical activity was measured throughout both courses by using a Philips DirectLife activity monitor.[29] Fasting blood samples (whole blood) were taken between 8 AM and 10 AM and were used to analyze lipid profiles (triglycerides, cholesterol, HDL, and LDL) and glucose and insulin levels.

Adverse Events

Adverse events, defined as any adverse change in condition between the first dose and 16 days after the last dose, were assessed in accordance with the US National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[30]

Statistical Analysis

Data were analyzed for carry-over effects and for period, that is, order of treatment, effects by using paired Student's t test—each patient served as his or her own control.[31] In each treatment course, a delta score, that is, the difference between two scores, was calculated by subtracting the score on treatment day 1 from the score on treatment day 5. The treatment effect was assessed by comparing the delta-placebo score with the delta-hydrocortisone score by using paired Student's t test with normally distributed values or the Wilcoxon signed-rank test. Adjusted P values (Benjamin-Hochberg procedure) are reported in the Data Supplement. A nested subset analysis was used to evaluate the effect of hydrocortisone in children who experienced clinically relevant dexamethasone-related adverse effects. Clinically relevant psychosocial adverse effects were defined as a change of ≥ 5 in parent-reported SDQ total difficulties score during the respective placebo course. This difference represents approximately one standard deviation in the general population.[22] Clinically relevant sleeping problems were defined as a change of ≥ 7 (one standard deviation) in the total SDSC score during the respective placebo course.[26,32] In the subset analysis, we examined the effect size rather than the P value because of the potential influence of regression to the mean in the subgroup selection.

RESULTS

Enrollment

During the recruitment period, 50 (49.5%) of 116 potentially eligible patients enrolled at the five pediatric oncology departments from July 2012 through February 2015. The most frequently cited reasons for not participating in the study were the high burden of two extra visits (37 patients) and an absence of a priori dexamethasone-related adverse effects (eight patients; Fig 2). After patients were randomly assigned to treatment groups, two patients left the trial after the first course as a result of dexamethasone-related osteonecrosis and were excluded from the efficacy analyses.

Treatment groups were similar with respect to age, type of leukemia, treatment protocol, and CNS status at diagnosis (Data Supplement). Two patients did not complete the parent-reported SDQs at all four time points and were therefore excluded from the efficacy analysis. Four patients developed serious adverse events after the first study course (two hydrocortisone courses and two placebo courses), with three of these patients developing febrile neutropenia (grade 2 to 3), and one patient developing osteomyelitis (grade 3). These serious adverse events were not considered related to study medication, and all four patients remained in the study. Adverse events were similar between the hydrocortisone and placebo courses, which indicated that no hydrocortisone-specific adverse events were observed (Data Supplement). No carry-over effect (P = .34; independent samples Student's t test) or period effect (P = .76; Mann-Whitney test) was observed on the basis of the primary outcome.

Psychosocial Problems

SDQ results obtained from 46 primary parents (41 mothers and 5 fathers) were analyzed to evaluate the psychosocial problems of the children. Four days of dexamethasone treatment significantly increased patient problems as reported by all SDQ scales and subscales. In 30 (65%) of 46 patients, dexamethasone induced an increase in psychosocial problems, defined as a ≥ 1-point change in the SDQ total difficulties score, during the placebo course. One third of the population did not have any increase in SDQ total difficulties with dexamethasone. Median SDQ total difficulties

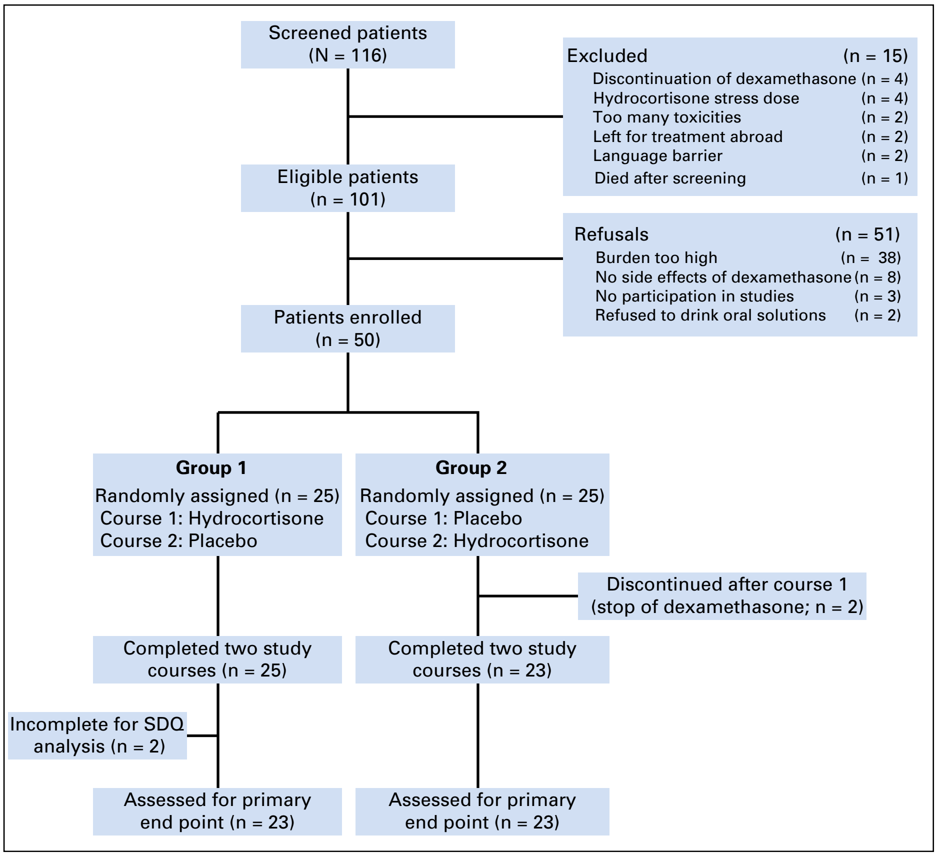

Fig 2. CONSORT diagram. SDQ, Strengths and Difficulties Questionnaire.

score of the entire study group on treatment day 5 in the placebo course was 9.5, which was within the normal range.

In the entire group, addition of hydrocortisone did not affect the total difficulties score (mean difference, −0.8 ± 5.5; *P* = .33), emotional symptoms (mean difference, −0.6 ± 2.3; *P* = .08), conduct problems (mean difference, 0.0 ± 1.5; *P* = 1.00), or other SDQ subscales compared with the placebo course (Fig 3).

However, when we examined the effect of hydrocortisone on the subset of 16 patients who had clinically relevant dexamethasone-related adverse effects, that is, an increase of ≥ 5 in their SDQ total difficulties score, we found that hydrocortisone had a clinically significant treatment effect. In these 16 children, hydrocortisone had a clear effect on the total difficulties delta-score compared with placebo (median difference, −5.0; IQR, −7.8 to −3.0; Fig 3). In five (31%) of 16 patients, total difficulties score decreased from a high score in the placebo course to a score in the normal range with the addition of hydrocortisone. We also observed a significant effect of hydrocortisone versus placebo on emotional symptoms (median difference, −1.5; IQR, −4.0 to −1.0), conduct problems (median difference, −1.0; IQR, −2.0 to 0.0), and impact of stress scores (median difference, −1.0; IQR, −2.0 to 0.0; Fig 3). Real SDQ scores and for point estimates (95% CI) of median differences are reported in the Data Supplement.

With respect to their baseline characteristics, the patient group with clinically relevant dexamethasone-induced adverse effects did not differ significantly from the group of patients without clinically relevant dexamethasone-induced psychosocial adverse effects. The week of maintenance phase in which the patients participated did not influence adverse effects (*P* = .47). Child-reported SDQ scores (n = 10) did not differ significantly from their respective parent-reported scores (*P* = .44).

Sleep

Parents of 47 children completed the SDSC questionnaire on all four testing days. Dexamethasone treatment alone, that is, the placebo course, significantly increased the disorders of arousal (*P* = .04), SWTD (*P* = .01) and DES (*P* = .01) scores. In the entire patient group, hydrocortisone had no significant effect on SDSC scores (SDSC total score: *P* = .84; DIMS: *P* = .74; DES: *P* = .29; SWTD: *P* = .29; Fig 4); however, when the nine children (19%) who had clinically relevant dexamethasone-induced sleeping problems, defined as a change of ≥ 7 in SDSC total score during the placebo course, were analyzed separately, hydrocortisone reduced both the SDSC total scores (median difference, −11.0; IQR, −16.0 to 0.0) and DIMS scores (median difference, −3.0; IQR, −7.0 to –0.5; Fig 4). The majority of patients with clinically relevant sleeping problems also experienced clinically relevant psychosocial adverse effects during dexamethasone treatment (n = 7; 78%).

Neuropsychological Functioning

Neuropsychological tests revealed that dexamethasone treatment alone had no effect on attention (auditory attention, response set, and inhibition), visual-spatial functions (design copying), memory (narrative memory and memory for designs), or processing speed; however, addition of hydrocortisone significantly improved

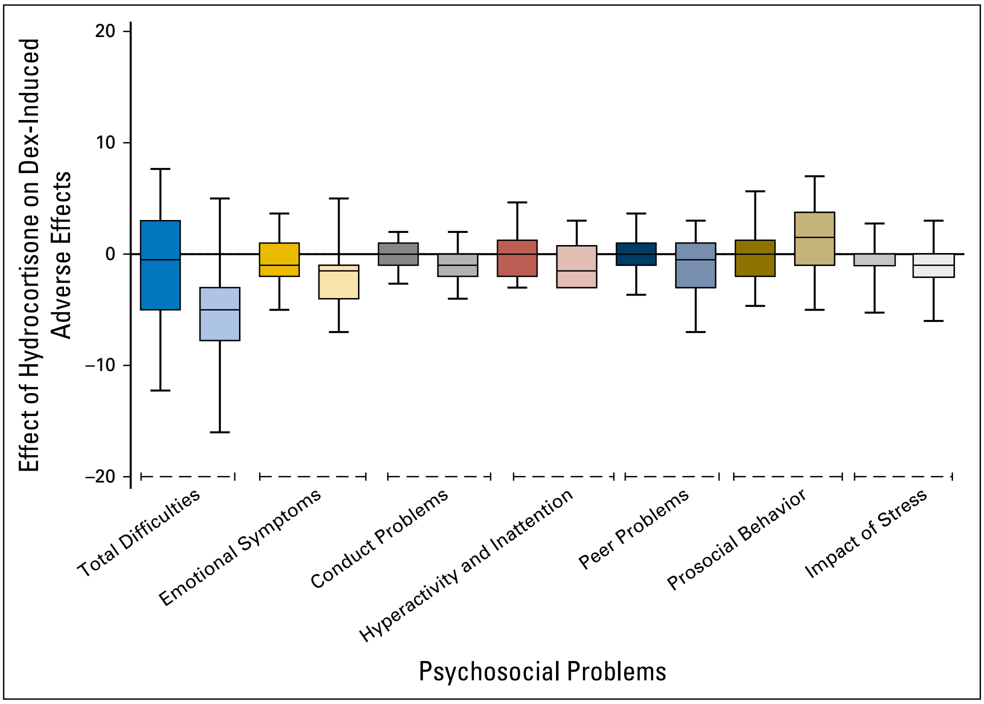

Fig 3. Effect of addition of hydrocortisone in the total group (n = 46; left bars with no pattern) and in patients with clinically relevant dexamethasone (Dex)-induced psychosocial adverse effects (n = 16; right bars with pattern) on Strengths and Difficulties Questionnaire (SDQ) subscales. Effect was measured by delta hydrocortisone minus delta placebo. (Delta, score treatment day 5 minus score treatment day 1.) Box-Whisker plots with median and 5-95 percentiles are depicted for each SDQ scale. A negative score reflects a decrease in adverse effects by hydrocortisone, with exception of the prosocial behavior score (positive score reflects fewer adverse effects).

long-term visual memory (*P* = .01; n = 47; Data Supplement). Hydrocortisone had no effect on other neuropsychological tests of attention, visual-spatial function (NEPSY [A Developmental Neuropsychological Assessment]), or processing speed (Wechsler; Data Supplement). The neuropsychological performance of the children with clinically relevant dexamethasone-induced psychosocial adverse effects was similar to the neuropsychological performance of the entire group.

Metabolism

Physical activity data measured by using BPAQ, were available for 36 patients, and activity monitor data were available for 41 patients. Physical activity was neither affected by dexamethasone nor by hydrocortisone addition.

Dietary intake and data regarding eating behavior measured by using DEBQ-C were available for 44 and 17 patients, respectively (Data Supplement). Hydrocortisone had no significant effect on energy intake (*P* = .88). Similarly, the addition of hydrocortisone had no significant effect on weight, height, waist-hip ratio, blood pressure, or any laboratory values (Data Supplement).

DISCUSSION

Here, we report the results of the first randomized controlled clinical trial, to our knowledge, to investigate whether a potentially safe intervention, that is, physiologic doses of hydrocortisone, can be used to reduce dexamethasone-induced neuropsychological

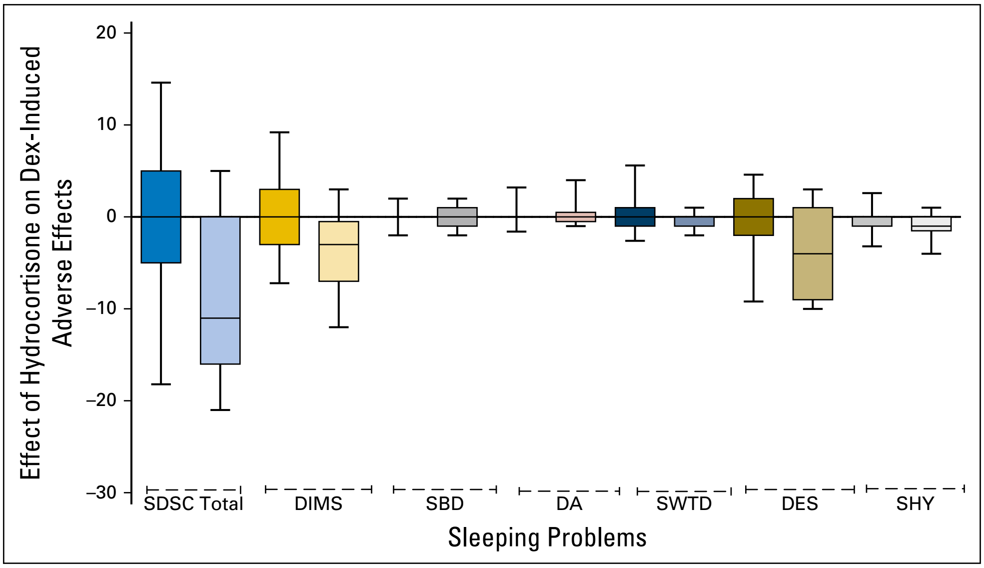

Fig 4. Effect of hydrocortisone addition in the total group (n = 47; left bars with no pattern) and in the patients who suffer from clinically relevant dexamethasone (Dex)-related sleeping problems (n = 9; right bars with pattern) on the Sleep Disturbance Scale for Children (SDSC) subscales. Effect was measured by delta hydrocortisone minus delta placebo. (Delta, score treatment day 5 minus score treatment day 1.) Box-Whisker plots with median and 5-95 percentiles are depicted for each SDSC scale. A negative score reflects a decrease in adverse effects by hydrocortisone. DA, disorders of arousal; DES, disorders of excessive somnolence; DIMS, disorders of initiating and maintaining sleep; SBD, sleep breathing disorders; SHY, sleep hyperhidrosis; SWTD, sleep-wake transition disorders.

adverse effects in pediatric patients with ALL. Both patients and their parents consider neuropsychological adverse effects to be the most detrimental consequences of ALL treatment with respect to the reduction in quality of life.[2] Our results show that although hydrocortisone had no significant beneficial effect in the entire patient group, hydrocortisone significantly decreased dexamethasone-related behavioral difficulties, emotional disorders, and sleep problems specifically in patients who experienced the most severe neuropsychological adverse effects. This finding is particularly relevant as psychosocial problems can be present in up to two thirds of children with ALL, and one half of the problems can be categorized as clinically relevant. Thus, our results indicate that these emotional and behavioral problems can be reduced in these children, thereby markedly improving quality of life.[33] Moreover, sleeping problems—one half of which were categorized as clinically relevant—have been reported in 43% of patients, and reducing these problems may also improve quality of life.[34]

Conversely, these findings suggest that adding hydrocortisone does not benefit all children with ALL. One third of the population did not have any neuropsychological adverse effects with dexamethasone treatment. This patient variability in adverse effects may be explained by genetics,[35] glucocorticoid sensitivity,[36] or dexamethasone clearance (higher drug levels).[37] Occurrence of neuropsychological adverse effects was independent of age, in contrast to Mrakotsky et al,[38] who reported more neurobehavioral problems in younger children. It should be mentioned that subgroups are small, and regression to the mean could have influenced our subgroup selection and that our results should be confirmed, preferably, in a validation study in selected patients with symptoms only; however, the substantial effect size of the intervention indicates a benefit of hydrocortisone in patients with psychosocial problems and sleeping problems.

Hydrocortisone addition did improve one specific memory score. As a result of the absence of acute dexamethasone-induced impairment of cognitive function, clinical relevance of this finding is limited. Absence of dexamethasone-induced short-term cognitive impairment is in accordance with the study of Wingenfeld et al[36] who did not find an effect of high-dose dexamethasone on working memory in healthy volunteers.

Of interest, hydrocortisone also had no effect on the metabolic adverse effects of dexamethasone. This lack of efficacy may be caused by a different pathophysiology of metabolic adverse effects. This notion is supported by the absence of a significant difference in body weight change during induction therapy—an important metabolic adverse effect of high dose glucocorticoids, for example, prednisolone—between children with neuropsychological adverse effects and children without neuropsychological adverse effects. It is conceivable that metabolic adverse effects are not caused by cortisol depletion of the cerebral MRs.

In conclusion, our current study suggests that including a physiologic dose of hydrocortisone decreases clinically relevant dexamethasone-induced psychosocial problems and sleeping problems in pediatric patients with ALL. For a validation study, it is important to identify patients who will benefit from hydrocortisone treatment by using SDQ-Dut and SDSC. Physiologic doses of hydrocortisone are relatively inexpensive, provide a naturally occurring hormone, and have no apparent negative effects. This novel, yet simple, intervention has the potential to significantly reduce neuropsychological adverse effects in patients who receive high-dose dexamethasone treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Hydrocortisone as an Intervention for Dexamethasone-Induced Adverse Effects in Pediatric Patients With Acute Lymphoblastic Leukemia: Results of a Double-Blind, Randomized Controlled Trial

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