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European Journal of Cancer 187 (2023) 124–133

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Hydrocortisone to reduce dexamethasone-induced neurobehavioral side-effects in children with acute lymphoblastic leukaemia—results of a double-blind, randomised controlled trial with cross-over design

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Received 10 March 2023; Accepted 29 March 2023
Available online 7 April 2023

KEYWORDS

Abstract ***Background:*** Dexamethasone is a cornerstone of paediatric acute lymphoblastic leukaemia (ALL) treatment, although it can induce serious side-effects. Our previous study suggests that children who suffer most from neurobehavioural side-effects might benefit from physiological hydrocortisone in addition to dexamethasone treatment. This study aimed to validate this finding.

Methods: Our phase three, double-blind, randomised controlled trial with cross-over design included ALL patients (3–18 years) during medium-risk maintenance therapy in a national

DOI of original article: http://dx.doi.org/10.1016/j.ejca.2023.112979, https://doi.org/10.1016/j.ejca.2023.112980
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https://doi.org/10.1016/j.ejca.2023.03.039

Dexamethasone;
Hydrocortisone;
Randomised controlled trial;
Neurobehavioral;
Sleep;
Quality of life

tertiary hospital between 17th May 2018 and 5th August 2020. A baseline measurement before and after a 5-day dexamethasone course was performed, whereafter 52 patients with clinically relevant neurobehavioural problems were randomised to receive an intervention during four subsequent dexamethasone courses. The intervention consisted of two courses hydrocortisone (physiological dose 10 mg/m2/d in circadian rhythm), followed by two courses placebo, or vice versa. Neurobehavioural problems were assessed before and after each course using the parent-reported Strengths and Difficulties Questionnaire (SDQ) as primary end-point. Secondary end-points were sleep problems, health-related quality of life (HRQoL), hunger feeling, and parental stress, measured with questionnaires and actigraphy. A generalised mixed model was estimated to study the intervention effect.

Results: The median age was 5.5 years (range 3.0–18.8) and 61.5% were boys. The SDQ filled in by 51 primary caregivers showed no difference between hydrocortisone and placebo in reducing dexamethasone-induced neurobehavioral problems (estimated effect -2.05 (95% confidence interval (CI) -6.00–1.90). Also, no benefit from hydrocortisone compared to placebo was found for reducing sleep problems, hunger, parental stress or improving HRQoL.

Conclusions: Hydrocortisone, when compared to placebo, had no additional effect in reducing clinically relevant dexamethasone-induced neurobehavioural problems. Therefore, hydrocortisone is not advised as standard of care for children with ALL who experience dexamethasone-induced neurobehavioural problems.

Trial registration: Netherlands Trial Register NTR6695/NL6507 (https://trialsearch.who.int/) and EudraCT 2017–002738–22 (https://eudract.ema.europa.eu/).

1. Introduction

The introduction of dexamethasone for the treatment of paediatric acute lymphoblastic leukaemia (ALL) significantly contributed to the current overall 5-year survival rate of more than 90% [1]. However, dexamethasone may cause severe adverse effects, of which emotional or behavioural disturbances and sleep problems are experienced as detrimental with respect to health-related quality of life (HRQoL) by both patients and parents [2,3]. Currently, in most paediatric ALL treatment protocols, dexamethasone is administered in monthly 5-day courses, during at least one and a half year of maintenance treatment, thereby significantly impacting well-being of child and family for a substantial amount of time. Children and parents can be supported through psychological interventions; however, no effective treatment to overcome dexamethasone-induced neurobehavioural problems exists to date [4,5].

The pathophysiology of dexamethasone-induced neurobehavioural problems is complex. Previous studies emphasised that both the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) in the brain play an important role in the regulation of mood, behaviour, and sleep [6,7]. The MR and GR are activated by binding of endo- and exogenous glucocorticoids. Dexamethasone has a high affinity for the GR, but in contrast to other glucocorticoids, binds the MR to a minimal extent [8]. Simultaneously, the endogenous production of cortisol, which has a high affinity for the MR, is suppressed due to the supra-physiological dose of dexamethasone [9]. Dexamethasone treatment may therefore lead to a relatively insufficient activation of the MR, and this can lead, as shown in preclinical studies in MR knockout mice, to increased anxiety behaviour [7]. In adults with major depression, treatment with MR antagonists was associated with impaired cognitive function and sleep [7]. Our hypothesis was that the relatively underactivated MR contributes to the dexamethasone-induced neurobehavioural side-effects observed in ALL patients [6,7,10].

Based on this hypothesis, we previously performed a double-blind, randomised placebo-controlled trial (RCT) in which we investigated whether neurobehavioural side-effects could be ameliorated by adding physiological dosages of hydrocortisone, to activate the MR in the brain [10]. The intervention suggested a beneficial effect of hydrocortisone, however only for the subset of children who suffered most from dexamethasone-induced neurobehavioural side-effects [10]. Since the results of this study were based on a relatively small number of patients with clinically relevant side-effects, we aimed to validate this finding in a larger targeted patient cohort. The current study therefore aimed to validate that hydrocortisone decreases dexamethasone-induced neurobehavioural problems in an independent cohort of children with ALL who suffer from these problems. Our secondary aims were to examine whether adding hydrocortisone could reduce dexamethasone-induced sleep problems and feeling of hunger, and improve patient HRQoL and parental stress [11].

2. Methods

2.1. Study design

This phase three, double-blind, placebo-controlled, RCT with cross-over design, the DexaDays-2 study, was conducted in the Princess Máxima Center for paediatric oncology in the Netherlands (national tertiary hospital). The study was approved by the Medical Ethical Committee of Rotterdam (NL62388.078.17) and was included in the Netherlands Trial Register (NTR6695/NL6507) [12]. Detailed methods have been published previously [11] and an additional relevant method section is available as Supplement.

2.2. Participants

Medium Risk Group (MRG) ALL patients, aged 3–18 years, treated according to the Dutch Childhood Oncology Group ALL-11 protocol who received dexamethasone during maintenance treatment were eligible. All included parents and/or patients gave written informed consent to participate in the study. Patients were assessed before and after one dexamethasone course, whereafter patients with an increase of ≥5 points (clinically relevant dexamethasone-induced problems) [10,13] on the parent-reported Strengths and Difficulties Questionnaire (SDQ) were eligible for the RCT (Fig. 1).

2.3. Intervention

The intervention consisted of oral physiological dosage of liquid hydrocortisone: 10 mg/m^2/d in a circadian rhythm; 5 mg/m^2 in the morning directly after awakening, 3 mg/m^2 in the afternoon and 2 mg/m^2 in the evening. Hydrocortisone was administered for five consecutive days, in addition to dexamethasone. Placebo was administered similarly and had the same appearance and taste as hydrocortisone. Patients were randomised using the method of a prefixed randomisation list, prepared by the pharmacy, to receive two courses hydrocortisone followed by two courses placebo, or vice versa (Fig. 1). The administration of study medication was blinded for physicians, parents, patients and research personnel.

At the close-out visit, parents were asked whether they thought their child had started with hydrocortisone or with placebo during the RCT.

2.4. Outcomes

The primary outcome was measured at all timepoints (T1-T10). Secondary outcomes were measured on T1/T2, T3/T4 and T7/T8, except for health-related quality

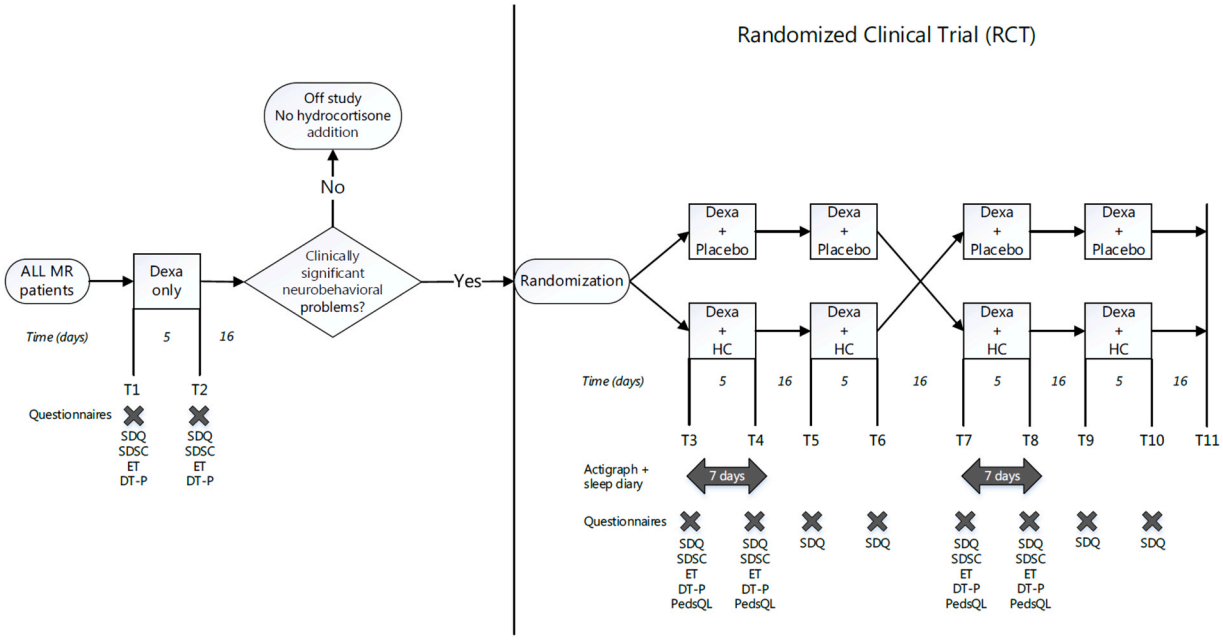

Fig. 1. DexaDays-2 Study Design. Eligible ALL patients were first enrolled to identify clinically relevant dexamethasone-induced neurobehavioural problems. Parents filled in several questionnaires before (T1) and after (T2) a 5 d 'dexamethasone only' treatment. If patients showed ≥5 points increase on the SDQ Total difficulties score, they were included in the RCT and subsequently randomised to start with either placebo or hydrocortisone. After two courses cross-over took place. Before and after each treatment block, parents filled in several questionnaires (T3-T10). During the first course of each treatment (hydrocortisone and placebo), patients also wore an actigraph to measure sleep objectively. T11 was used as a close-out visit. Abbreviations: ALL, acute lymphoblastic leukaemia, dexa, dexamethasone; DT-P, distress thermometer for parents; ET, eating thermometer; HC, hydrocortisone; MR, medium risk; PedsQL, paediatric quality of life questionnaire; RCT, randomised placebo-controlled trial; SDSC, sleep disturbance scale for children; SDQ, Strengths and Difficulties Questionnaire.

of life and objective sleep through actigraphy, which were measured at T3/T4 and T7/T8 only, to minimise patient burden (Fig. 1).

2.4.1. Primary outcome

2.4.1.1. Neurobehavioural problems

To answer our primary aim, we used the Dutch version of the parent-reported SDQ [13–17]. This 25-item questionnaire assesses psychological adjustment of children and youths and provides five subscales: emotional symptoms, conduct problems, hyperactivity and inattention, peer relationship problems, and prosocial behaviour. The Total difficulties score is the sum of the first four subscale scores (i.e. without prosocial behaviour), a higher score reflects more problems.

2.4.2. Secondary outcomes

2.4.2.1. Sleep problems

Children wore a wrist-worn actigraph (ActiGraph wGT3X-BT, Pensacola, FL, USA) for seven consecutive days twice: once during hydrocortisone and once during placebo (Fig. 1). The parent kept an additional sleep diary. To assess subjective sleep quality and sleep disturbances, we used the Sleep Disturbance Scale for Children (SDSC) [18]. This questionnaire contains 26 items and yields six subscales and a Total sleep score: a higher score reflects more problems.

2.4.2.2. Hunger score

To measure dexamethasone-induced feeling of hunger, we used an Eating Thermometer (ET): a visual analogue scale to indicate hunger [19,20]. Four different thermometers were administered: to indicate average, least and worst hunger the past 24 hours, and fasting feeling of hunger. The scale ranged from 0 (no hunger at all) to 10 (terrible hunger).

2.4.2.3. Health-related quality of life

The Pediatric Quality of Life Inventory (PedsQL), a 21- (for toddlers) or 23-item questionnaire, was used to assess HRQoL [21]. A higher score reflects a better HRQoL in the child.

2.4.2.4. Parental distress

We used the Distress Thermometer for parents (DT-P) to assess parental distress [22]. Parents were asked to rate their overall distress from 0 (no distress) to 10 (extreme distress).

2.5. Adverse events

All adverse events, defined as any change in condition between the very first dose and 16 d after the last dose of study medication, were recorded consistent with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [23].

2.6. Statistical analysis

Descriptive statistics for baseline characteristics with either means and standard deviations or medians with interquartile ranges, depending on distribution, were calculated. Comparison of baseline characteristics between included patients and not included patients was done with χ^2 test or Mann-Whitney U test in case of violation of normality assumption.

First, the data was analysed for carry-over effect or period effect (i.e. the order of treatment), using a paired-samples T-test or Mann-Whitney U test. To assess the effect of hydrocortisone on neurobehavioural problems we calculated delta SDQ scores by subtracting the SDQ score at the start of a dexamethasone course, from the SDQ score after five days of dexamethasone (e.g. T6-T5 or T4-T3, Fig. 1). These delta scores were compared using the Wilcoxon-signed-rank test, as was described in our study design [11]. Furthermore, due to the presence of repeated measures, a generalised mixed model was estimated to study the effect of hydrocortisone. Included covariates were age, sex, start group (hydrocortisone/placebo), week of maintenance treatment, concomitant asparaginase treatment (yes/no) [24], and whether mother or father completed the questionnaire [25]. An interaction term between intervention and time was also included. To assess the effect of hydrocortisone compared to placebo, we estimated a mixed model for timepoints T3 to T10. The toeplitz covariance matrix structure was used in the model since the within subjects' correlation gets weaker for times further apart.

Subscores and secondary outcomes were analysed in a similar way as described above. A decrease on the SDQ Total Difficulties score of 5 points (1 standard deviation (SD) of the norm) was considered clinically significant. A p-value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 26.0.

3. Results

Of 256 newly diagnosed ALL patients (17th May 2018 till 5th August 2020), 123 patients were eligible, of whom 79 gave informed consent to participate. The most common reported reason for refraining from participation was the burden and time-consuming nature of the study (38%). Of the 79 included patients, 52 (66%) experienced clinically relevant dexamethasone-induced side-effects and were therefore eligible for the RCT and subsequently randomised to start with hydrocortisone (n = 26) or placebo (n = 26) (Fig. 2).

Median age at the start of the RCT was 5.5 years (range 3.0–18.8) and 61.5% were boys. The randomised subgroups (hydrocortisone or placebo first) did not differ significantly with respect to baseline characteristics and baseline questionnaire measurements. The total group (n = 79), patients who refused to participate

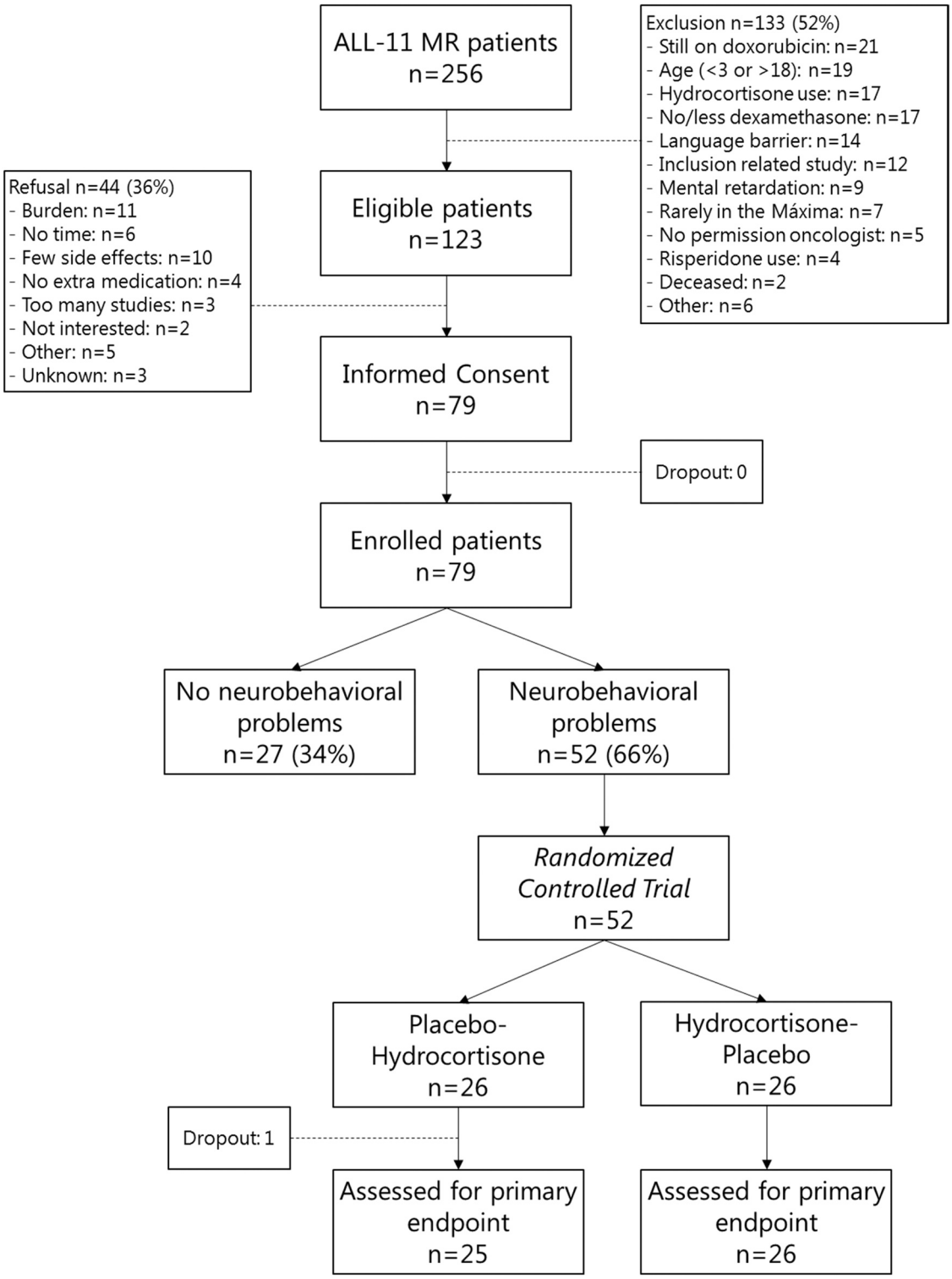

Fig. 2. CONSORT flow diagram. ALL patients were screened on our in- and exclusion criteria and after approval of the treating paediatric oncologist approached for inclusion. Reasons for refusal are what parents or patients themselves reported. After enrolment, patients were measured during a 'dexamethasone only' course. Patients with clinically significant neurobehavioural problems were subsequently included in the randomised controlled trial. Due to one dropout 26 children who started with hydrocortisone and 25 children who started with placebo were assessed for our primary end-point. Abbreviations: ALL, acute lymphoblastic leukaemia; MR, medium risk.

Table 1
Difference in neurobehavioural side-effects measured with the SDQ

		Randomised controlled trial		
n = 51 median (IQR)	Δ *score dexa only*	*Average Δ 2 courses hydrocortisone*	*Average Δ 2 courses placebo*	**Hydrocortisone versus placebo** estimated effect (95% CI)
Total difficulties	12.0 (8.0; 15.0)	5.0 (2.0; 9.0)	5.8 (3.0; 9.0)	−2.05 (−6.00; 1.90)
Emotional problems	4.0 (3.0; 6.0)	1.5 (0.5; 3.0)	2.0 (1.5; 3.5)	−0.94 (−2.49; 0.60)
Conduct problems	2.0 (1.0; 3.0)	1.0 (0.5; 2.0)	1.0 (0.0; 2.0)	−0.32 (−1.54; 0.89)
Hyperactivity	4.0 (2.0; 5.0)	1.5 (0.0; 3.0)	2.0 (1.0; 4.0)	−1.64 (−3.29; 0.01)
Peer problems	2.0 (1.0; 3.0)	1.0 (0.0; 2.0)	0.5 (0.0; 1.5)	0.88 (−0.18; 1.93)
Prosocial	−4.0 (−5.0; −2.0)	-2.0 (−3.5; −0.5)	−2.0 (−3.0; −1.0)	−0.37 (−1.85; 1.10)

Delta scores are calculated for the SDQ Total difficulties score and all subscales by subtracting day 1 (start dexamethasone course) from day 5 (end of dexamethasone course) scores. Hydrocortisone and placebo were added during two subsequent courses, for these courses the average delta score was calculated. The estimated effect is corrected for age, sex, start group (hydrocortisone/placebo), week of maintenance treatment, concomitant asparaginase treatment (yes/no), whether mother or father completed the questionnaire and an interaction term between intervention and time.
Abbreviations: 95% CI, 95% confidence interval, dexa; dexamethasone; IQR, interquartile range; SDQ, strengths and difficulties questionnaire.

(n = 44), as well as the included patients who were not eligible for the RCT (n = 27), were not statistically different with regard to baseline characteristics either (Supplemental Table 1). There was no carry-over effect ($p = 0.49$), nor a period effect ($p = 0.77$) in our study, based on the primary outcome.

3.1. Primary outcome: neurobehavioural problems

The median increase in SDQ Total Difficulty score (delta SDQ) during 'dexamethasone only' was 12 points (interquartile range (IQR) 8–15). During hydrocortisone courses the median delta SDQ was 5 points (IQR 2–9) and during placebo courses 6 points (IQR 3–9) (Table 1). There was no statistically significant difference between hydrocortisone and placebo in reducing dexamethasone-induced neurobehavioural problems ($p = 0.33$). The mixed model analysis showed the same trend: estimated effect hydrocortisone compared to placebo −2.05 (95% CI −6.00–1.90) (Fig. 3, Table 1, Supplemental Table 2).

None of the covariates included in the model were associated with the primary outcome. The findings were consistent in the analyses of the SDQ subscores, however with smaller estimated effects (Table 1, Supplemental Table 2).

At the end of the study period for each individual child, parents indicated whether they thought their child had started with placebo or hydrocortisone. Of 52 parents, 24 (46%) were correct, 24 (46%) were not, and four parents (8%) were unsure.

3.2. Secondary outcomes

In total, 75 actigraphy weeks of 39 children were available for analysis. The main reason for missing data was the child refusing to wear the Actigraph (n = 11). No statistically significant difference in any sleep outcome between hydrocortisone and placebo was observed (Supplemental Table 3).

The median delta SDSC Total score (n = 42) was 11 points (IQR 6–18) in 'dexamethasone only' course, and 4 (IQR 1–10) and 3 (IQR 1–8) in the hydrocortisone and placebo courses, respectively. There was no significant difference between hydrocortisone and placebo (Fig. 4a, Supplemental Table 4). Results did suggest that parents reported less sleep problems if their child was further in maintenance treatment (Supplemental Table 5).

The median delta most extreme hunger score (n = 38) was 2 points during 'dexamethasone only' (IQR 2–4), 2 points during hydrocortisone (IQR 1–4) and 2 points during placebo (IQR 1–3). Results showed that hydrocortisone led to an increased average and fasting hunger score compared to placebo (Fig. 4b, Supplemental Tables 4 and 6).

The median delta PedsQL score (n = 41) was −14 points (IQR −24 to −4) during hydrocortisone and −15 points (−26 to −7) during placebo, a difference which was not statistically significant (Fig. 4c, Supplemental Tables 4 and 7).

The delta distress thermometer score (n = 40) was 2 (IQR 1–4) during 'dexamethasone only' and the hydrocortisone and placebo courses, no difference between hydrocortisone and placebo in reducing parental distress was found (Fig. 4d, Supplemental Tables 4 and 8).

3.3. Adverse events

All adverse events (AEs) are depicted in Supplemental Table 9. Overall, adverse events were usually minor (grade 1 or 2) and equally divided between hydrocortisone and placebo periods. Most serious adverse events (SAEs) were scored as being related to leukaemia treatment (Supplemental Table 10). However, one patient left the study during the third study course due to abnormal behaviour (CTCAE grade 2). The mother described that her daughter became angry, delusional and associative after starting study medication. Therefore, after 2.5 days, her study medication was discontinued, her behaviour normalised, and deblinding

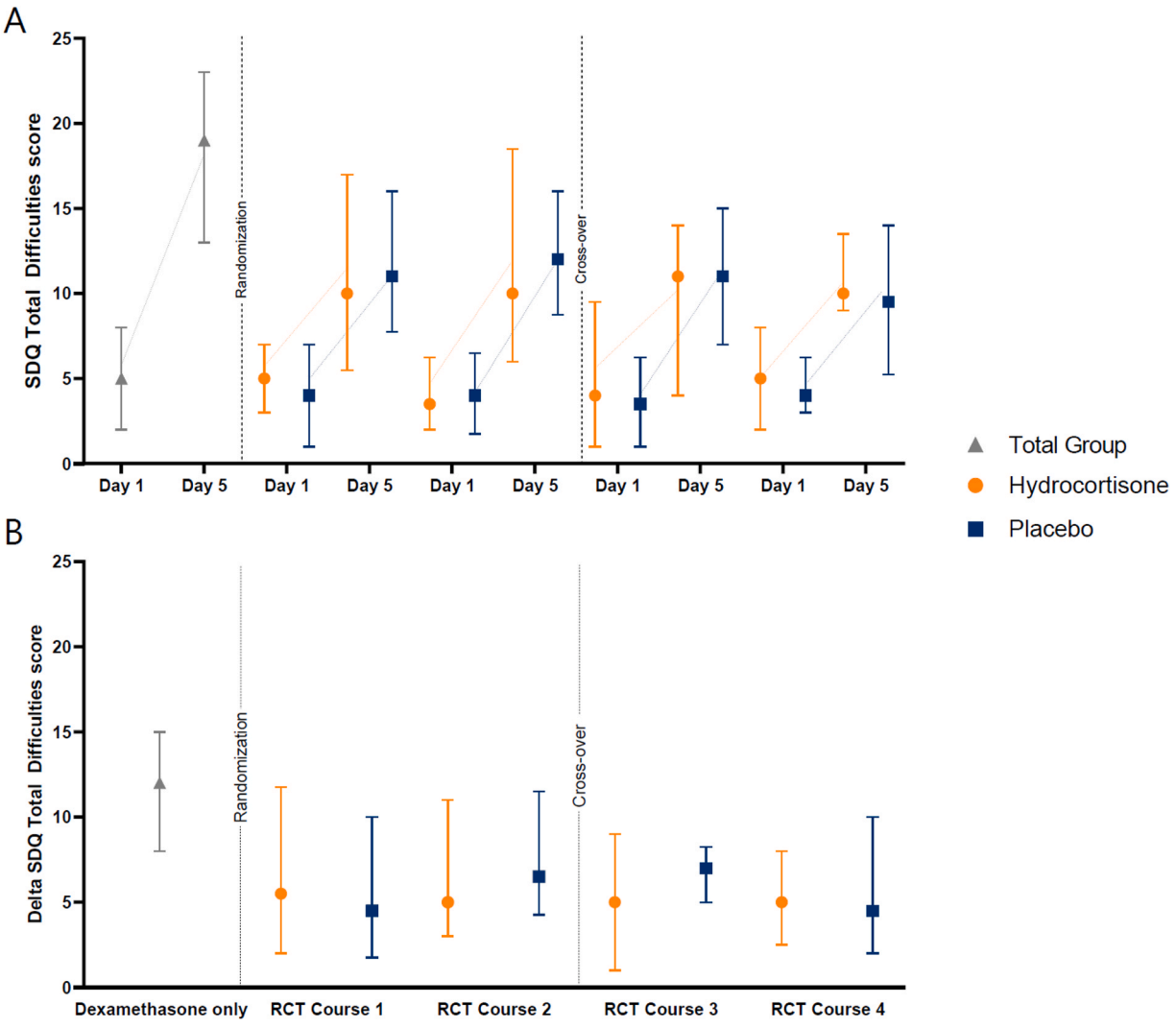

Fig. 3. Effect of hydrocortisone and placebo on dexamethasone-induced neurobehavioral problems. A) SDQ Total difficulties scores (median with IQR) on day one (start dexamethasone) and day 5 (stop dexamethasone). Grey triangles represent the total group (n = 51) during the 'dexamethasone only' course. During the RCT, patients who receive hydrocortisone or placebo (n = 25 or n = 26) are indicated with orange circles or blue squares, respectively. B) Delta SDQ Total difficulties score (median with IQR) of the total group (n = 51) is indicated in a grey triangle. After randomisation patients who receive hydrocortisone or placebo (n = 25 or n = 26) are indicated with an orange circle or a blue square, respectively. Abbreviations: IQR, interquartile range; SDQ, strengths and difficulties questionnaire; RCT, randomised clinical trial. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

took place for this patient. The study medication was hydrocortisone, and the episode was reported as an SAE, possibly related to the study medication.

4. Discussion

Our study showed that hydrocortisone, when compared to placebo, had no additional effect in reducing clinically relevant dexamethasone-induced neurobehavioural problems in children with ALL. Similarly, hydrocortisone was not better in reducing dexamethasone-induced sleep problems, feeling of hunger, parental distress or improving quality of life as compared to placebo.

The finding that, when compared to placebo, hydrocortisone did not significantly reduce dexamethasone-induced neurobehavioural problems was surprising, since our previous RCT suggested a beneficial effect of hydrocortisone [10]. Several choices in the current study design may have contributed to this different outcome. First, we selected patients with a rise of ≥5 points on the SDQ during a 'dexamethasone only' course, whereas the previous study did a post-hoc analysis on selected patients with a rise of ≥5 points during a placebo course. The results of the previous study may have been based on regression to the mean, rather than an effect of hydrocortisone. Second, we increased the inclusion age to 18 years, compared to 16 in the former study. This may have

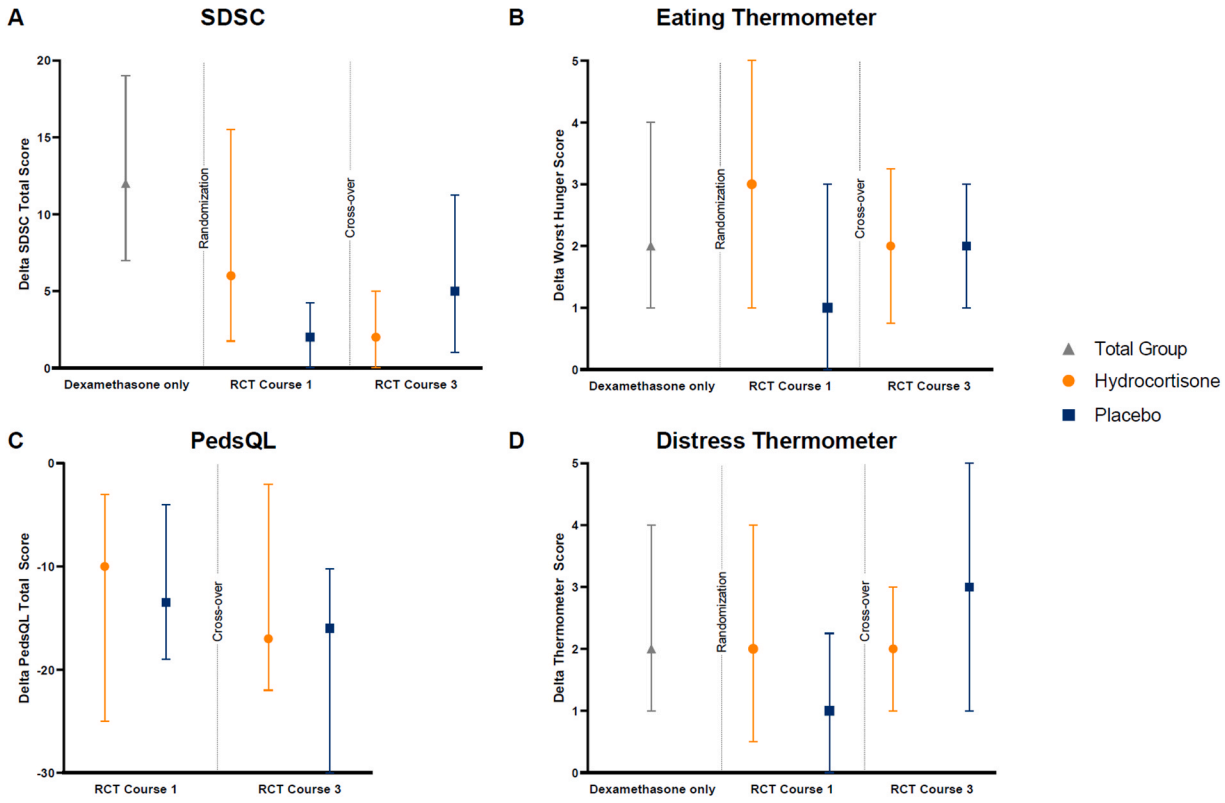

Fig. 4. Effect of hydrocortisone and placebo on (dexamethasone-induced) sleep problems, feeling hungry, quality of life and parental distress. The total group (n = 51) during a 'dexamethasone only' course is indicated with a grey triangle. After randomisation patients who receive hydrocortisone are indicated with an orange circle, and patients who receive placebo are indicated with a blue square (n = 26 or n = 25). (A) Delta SDSC Total score (median with IQR). (B) Delta Worst Hunger score (median with IQR). (C) Delta PedsQL total score (median with IQR). The PedsQL was only measured during the RCT. (D) Delta Thermometer score: Parental distress measured with the Distress thermometer for parents (median with IQR). Abbreviations: IQR, interquartile range; SDSC, sleep disturbance scale for children; PedsQL, paediatric quality of life (questionnaire); RCT, randomised clinical trial. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

influenced our results, since older children may have a lower risk of behavioural problems [26]. Nevertheless, only three patients older than 16 were included in our study. A third difference was the presence of two courses hydrocortisone and placebo instead of one, by which we aimed to mimic the repetitive dexamethasone courses with an often changing burden of side-effects. We accounted for the presence of repeated measurements by using a generalised mixed model to estimate the effect of hydrocortisone on the outcomes. This is a different analysis than the previously published study where the Wilcoxon-signed-rank test was used.

Due to our nationalised paediatric cancer care, more extensive information about side-effects of dexamethasone and experiences from other patients and parents may have influenced our results, illustrated by the fact that 66% of the included patients experienced clinically significant side-effects, in contrast to 35% in our previous study [10]. Previous negative experiences, worrisome information, mistaken beliefs and negative expectations induced by verbal suggestions are known to increase or even cause side-effects, and are described as *nocebo*-effects [27–29]. This nocebo-effect (by proxy) [30] of dexamethasone may have played an important role in our findings. In children, nocebo-effects can be severe and often anticipatory [31]. Behavioural and anticipatory adjustment of both child and family, may give rise to intensified behavioural changes. Hence, despite the fact that informing parents and children regarding side-effects is standard of care, overextended information may provoke non-intended adverse effects.

The secondary outcomes of this study were sleep, quality of life, and hunger feeling. Hydrocortisone did not reduce parental distress or improve sleep problems or quality of life of patients. Additionally, the average hunger score and fasting hunger score increased during hydrocortisone compared to placebo. The effect of glucocorticoids on hunger is not completely unravelled, and our findings may be explained by the fact that glucocorticoids act differently on appetite than on other side-effects, for example by altering excretion of appetite-regulating hormones, such as leptin [32]. Besides a different mechanism, a bias in reporting the hunger score could play a role since this proved to be difficult for parents, resulting in fewer patients to evaluate.

An interesting observation in our data is that the delta scores of the first, 'dexamethasone only' course are remarkably higher than the subsequent delta scores in the RCT (Figs. 3 and 4, Table 1 and Supplemental Table 4). This may be caused by regression to the mean, however other explanations may be possible. The decrease in side-effects during the RCT may be attributed to a placebo (by proxy) effect [29,30,33]. Expectancies, which are an important learning mechanism and may steer placebo-effects [34], may have played a role in our study, since both parents and children were informed about the potential positive effect of hydrocortisone. Furthermore, a participation effect or classical conditioning may have occurred: by adding an oral suspension to standard treatment, patients can be triggered to show physiological responses to additional medication [29,35–37]. However, since we did not include a third observational arm with treatment as usual, a direct comparison between the intervention with hydrocortisone or placebo and no intervention (natural course) cannot be made.

4.1. Clinical implications and future directions

The question remains, should we use hydrocortisone in clinical practice? Our study suggests that hydrocortisone has the same effect as placebo on the outcome. Therefore, hydrocortisone is not advised as standard of care for children with ALL who experience dexamethasone-induced neurobehavioural problems. The current study was not designed including a third 'treatment as usual' arm, therefore we cannot show that both hydrocortisone and placebo improve side-effects compared to a non-intervention setting. Based on the observations in our study, it would be interesting to explore the possibilities of nocebo- and placebo-effects in the respective prevention and treatment of dexamethasone-induced side-effects. A recent expert consensus paper regarding placebo- and nocebo-effects in adults stresses the importance of making optimal use of placebo-effects to achieve better treatment outcomes [38]. Studying the effect of hydrocortisone and open-label placebo, which has been proven effective in children with functional abdominal pain or attention deficit hyperactivity disorder (ADHD), would be very interesting [37,39]. Besides further research on the placebo-effect, we propose to create awareness about possible nocebo-effects of dexamethasone in clinical practice.

Funding

This study was funded by the non-profit organisation Kinderen Kankervrij (KiKa), project number 268.

KiKa had no role in the design or execution of this study, in the analyses or interpretation of the data, in writing of the manuscript nor in the decision to submit results.

CRediT authorship contribution statement

Annelienke M. van Hulst: Data curation, Formal analysis, Investigation, Project administration, Visualization, Writing - original draft, Writing - review & editing. **Erica L.T. van den Akker**: Conceptualization, Writing - review & editing, Supervision, Funding acquisition. **Emma J. Verwaaijen**: Investigation, Writing - review & editing. **Marta Fiocco**: Methodology, Formal analysis, Validation, Writing - review & editing. **Niki Rensen**: Investigation, Writing - review & editing. **Raphaële R.L. van Litsenburg**: Methodology, Writing - review & editing. **Saskia M.F. Pluijm**: Methodology, Writing - review & editing. **C. Michel Zwaan**: Resources, Writing - review & editing. **Hanneke M. van Santen**: Writing - review & editing. **Rob Pieters**: Resources, Writing - review & editing. **Andrea W.M. Evers**: Writing - review & editing. **Martha A. Grootenhuis**: Conceptualization, Writing - review & editing, Supervision, Funding acquisition. **Marry M. van den Heuvel-Eibrink**: Conceptualization, Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Prof. Dr. R. Pieters is editorial member of European Journal of Cancer. The authors declare no competing interests.

Acknowledgements

The authors would like to thank KiKa for funding this study (project number 268) and patients and parents for their participation in this study, plus all onsite personnel who contributed. Furthermore, we thank www.dewonderlijkereis.nl for the ongoing donations to research on dexamethasone-induced side-effects.

The authors also acknowledge Dr. Frederike Engels for her support with the study medication, Drs. Ria Koolma for database support, Drs. Femke Verwer for supporting the management of the trial and Drs. Esther van den Bergh for her expert advice regarding implementation of the results.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.03.039.

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