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ORIGINAL RESEARCH ARTICLE

Dexmedetomidine for prevention of opioid/benzodiazepine withdrawal syndrome in pediatric intensive care unit: Interim analysis of a randomized controlled trial

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Abstract

Study Objective: Withdrawal syndrome (WS) may be a critical drawback of opioid/benzodiazepine weaning in children. The most effective intervention to reduce WS prevalence is yet to be determined. Dexmedetomidine (DEX) was estimated to be effective in reducing WS-related symptoms, but no randomized trial has been conducted to prove its efficacy so far.

We aimed to evaluate the efficacy and safety of DEX in reducing the occurrence of WS.

Design and Setting: This was an adaptive randomized double-blind placebo-controlled trial conducted at three Italian Pediatric Intensive Care Units (PICUs).

Patients: It included children admitted to PICU, undergoing at least five days of opioids/benzodiazepines continuous infusion, and ready to start the analgosedation weaning.

Intervention: Twenty-four hours before the start of weaning, an infusion of DEX/placebo was started. WS symptoms were monitored using the Withdrawal-Assessment-Tool-version-1 (WAT-1). In case of WS symptoms (WAT-1 ≥ 3) an opioid/benzodiazepine bolus was given and the DEX/placebo infusion-rate was increased.

Measurements: The primary outcome measure was the prevalence of WS. Secondary outcomes were the trend of WAT-1 over time, number of rescue doses, length of weaning and PICU-stay, and onset of adverse events (AEs).

Main Results: Forty-five patients were enrolled, of whom 5 dropped-out and 40 entered the interim analysis. There were no significant baseline differences between groups. WS prevalence did not significantly differ between groups (77.8% DEX vs 90.9% placebo, $p = 0.381$). By generalized linear mixed modeling, the WAT-1 trend showed a significant increase per unit of time in the DEX arm (estimate 0.27, CI

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0.07–0.47, $p = 0.009$) compared to placebo. Most frequent AEs were hemodynamic, and all of them happened in the DEX arm.

Conclusions: A continuous infusion of DEX, started 24 h before the analgosedation weaning and increased based on WS signs, was not able to significantly modify the prevalence of WS in children who received at least five days of opioids/benzodiazepines treatment compared to placebo.

KEYWORDS
benzodiazepine, dexmedetomidine, intensive care unit, opioid, pediatric, sedation, withdrawal syndrome

1 | INTRODUCTION

Withdrawal syndrome (WS) is a critical sequela of analgesia and sedation treatments which may occur during the weaning phase of these medications in patients who had developed physical dependence.[1] Its incidence can reach up to 65% among patients who received more than 5 days of analgosedation.[2] Signs and symptoms of WS may add further complications to the severity of the critical illness of children in the pediatric intensive care unit (PICU), prolong the PICU stay, and significantly affect patient outcomes.[3]

Several studies have focused on identifying predictors of WS in order to improve its prevention strategies. Critically ill children who have received high doses of opioids and benzodiazepines for 3–5 days or longer are at greater risk of developing WS.[4] More recently, several other variables have been listed as risk factors for WS such as age less than 6 months, pre-existing cognitive impairment, administration of multiple classes of sedatives, and the care received from nurses with high workload or who are inadequately trained.[5] Among prevention strategies, a gradual tapering of analgosedation drugs, not exceeding 20% for each consecutive day, has been recommended, although gradual tapering often fails when used as the only strategy.[6] Switching to drugs with a long half-life, such as methadone, was reported to be successful in isolated studies, but strong evidence is still lacking.[7]

Dexmedetomidine (DEX), an alpha-2 adrenergic receptor selective agonist, has been proposed to be effective in controlling WS-related behavior symptoms and blunting sympathetic reactions.[8-10] Promising results have been described, albeit based only on limited observational studies.[11-13] However, to our knowledge, no randomized controlled trial (RCT) has been conducted so far to prove the efficacy of DEX in preventing WS. Here, we aimed to evaluate the efficacy of DEX in reducing the prevalence of opioid/benzodiazepine WS in a cohort of pediatric critically ill patients. The trial has been designed following an adaptive strategy, so that early results may guide early discussion and sample size reassessment. As a secondary aim, we sought to assess the safety of DEX in this specific setting.

2 | METHODS

2.1 | Study design, setting, and ethical approval

We conducted an adaptive, multicenter, randomized, double-blind, placebo-controlled, superiority clinical trial with two parallel groups. The study involved three tertiary-care academic PICUs. The Study Protocol was approved by the Ethics Committee of the University-Hospital of Bologna IRCCS S. Orsola Polyclinic (CE 167/2016/O/Sper), authorized by the Italian-Medicines-Agency (AIFA), and registered in Eudra-CT-Register (N. 2015-002114-80) as well as ClinicalTrials.gov (NCT03645603).[14] An independent Data-and-Safety-Monitoring-Board (DSMB) was nominated to oversee the trial progress. Detailed methods were previously published and are reported in the File S1 (Appendix S1).[14]

2.2 | Study population

We included all consecutive children aged from 7 days to 18 years, admitted to the PICU and being mechanically ventilated, who met also the following inclusion criteria: gestational age ≥37 weeks, had received at least 5 days of opioids and/or benzodiazepines infusion, were ready to start the analgosedation weaning, and had parents' written informed consent. We excluded patients with hemodynamic instability, inotropic or antihypertensive treatments, atrio-ventricular block, persistent fever of unknown origin, history of malignant hyperthermia, known hypersensitivity to alpha-agonists, or those who had used alpha-agonists in the 30 days preceding the study enrollment.

2.3 | Interventions

Patients were randomly assigned to one of the two treatments groups (randomization details are included in the Appendix S1). Figure 1 summarizes the study structure. Twenty-four hours before the start of the weaning, a continuous infusion of DEX or placebo

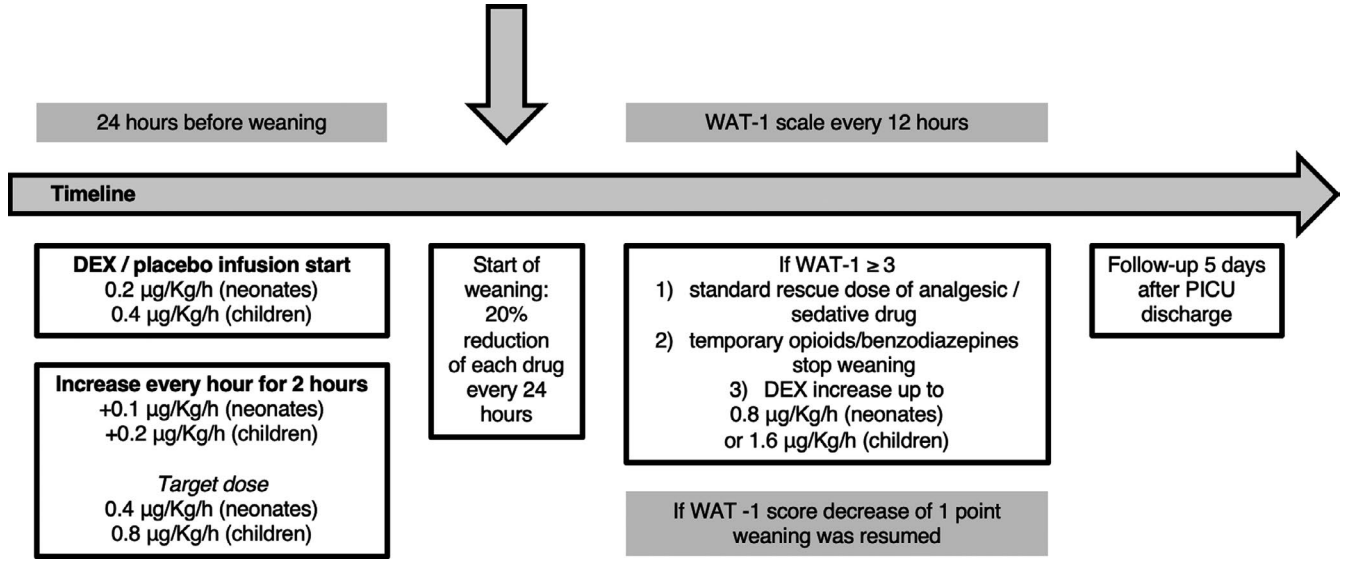


FIGURE 1 Study protocol and timeline. Abbreviations: DEX, dexmedetomidine; PICU, Pediatric Intensive Care Unit; WAT-1, withdrawal assessment tool-1

was started and gradually increased up to 0.8 µg/kg/h (0.4 µg/kg/h in neonates) within the first 2 h of infusion. Once the target rate was reached, the infusion was maintained for 24 h before starting the opioid/benzodiazepine weaning. Symptoms of WS were monitored every 12 h using the withdrawal assessment tool version 1 scale (WAT-1).[15] At any point, the WAT-1 score reached a value ≥3, clinicians were asked to administer a standard rescue dose of opioid and/or benzodiazepine, and increase the DEX/placebo dose by 0.2 µg/kg/h (0.1 µg/kg/h in neonates). If the following WAT-1 score (at 12 h from the previous one) showed a decrease by at least 1 point compared with the preceding one, the weaning was resumed with the same scheme, and the DEX/placebo infusion was maintained at the increased dose. Otherwise, the DEX/placebo infusion dose was increased up to a maximum of 1.6 µg/kg/h (0.8 µg/kg/h in neonates). The DEX/placebo infusion was finally weaned when all the opioid/benzodiazepine infusions were weaned off. A follow-up visit was performed 5 days after the PICU discharge to evaluate the length of DEX/placebo weaning, presence of withdrawal symptoms after discharge, onset of adverse events (AEs), and occurrence of DEX rebound/withdrawal symptoms after the DEX/placebo discontinuation.

2.4 | Outcome measures

The primary outcome measure was the prevalence of WS (i.e., WAT-1 ≥3) among patients treated with DEX compared with patients treated with placebo. Secondary outcome measures were the trend of WAT-1 score over time, the number of rescue doses administered, the length of opioid/benzodiazepine weaning, and the length of PICU stay. Additionally, as a secondary/sensitivity analysis, we measured the prevalence of WS with a more conservative definition of WS (i.e., WAT-1 ≥5). Safety was assessed by close monitoring of hemodynamic parameters and recording of any AEs potentially related to the treatment. Hemodynamic parameters (heart rate, systolic, and diastolic blood pressures) were considered altered if differing more than 20% compared to patient's baseline.

2.5 | Data collection and management

Clinical, demographic, and sedation characteristics, as well as WAT-1 score, were collected by investigators blinded to the treatment. All data were treated anonymously and with respect to data protection. Details of this process are described in the File S1 (Appendix S1).

2.6 | Statistical analysis

2.6.1 | Sample size and interim analysis

The sample size calculation was computed using an adaptive approach based on a two-stage Group Sequential Design with an interim sample size reassessment in order to compensate for discrepancies between expected and observed incidence of the WS rate at the first stage.[16] Details of the sample size calculations are described in the Appendix S1. After reaching the sample size for the interim analysis (i.e., $n = 40$), the treatment efficacy was evaluated in the Intent-to-Treat (ITT) population using the Z test statistics in order to compare the aforementioned primary outcome measure (prevalence of WS, with WS defined as WAT-1 ≥ 3) between the two treatment groups. The conditional power (CP) was found to be 0.25 (i.e., lower than 0.3), which required a sample size

reassessment. A sample size re-estimation assessment was equal to 308 patients (Table S1). The DSMB was, therefore, consulted and a decision was made to early terminate the trial for futility reasons.

2.6.2 | Data analysis

A detailed statistical analysis was performed on the sample reached at the time of the interim analysis. Continuous data were reported as median and I, III quartiles, and categorical data reported as absolute frequencies and percentages. Patients' and sedation characteristics were compared between the two intervention groups. The Wilcoxon-rank test was used to compare continuous variables, and the Pearson Chi-square test, or the Fisher-exact test when appropriate ($n < 5$ in >20% cells), was used for comparison of categorical variables. Generalized Linear Mixed Model (GLMM) with random intercept and Restricted Cubic Spline methods for modeling the non-linearities were used to model longitudinal WAT-1 data over time in the two intervention groups (Appendix S1). A two-side alpha level <0.05 was set as significant. All statistical analyses were performed using R statistics (version 3.6.2., R Core Team).[17]

3 | RESULTS

3.1 | Study population

From August 30, 2018 to January 18, 2020, 1278 patients were admitted to the three PICUs. At the time of the interim analysis, 1233 patients were excluded while 45 met the inclusion criteria and were enrolled (Figure 2). Five patients discontinued the study prematurely: two experienced significant changes in their clinical needs (one in the placebo arm and one in the DEX arm), and three showed hemodynamic AEs (heart rate and/or blood pressure decreased >20% compared to patient baseline values) a few hours after the introduction of DEX with need for infusion discontinuation (all in the DEX-arm). All three patients with hemodynamic AEs were infants weighing 5–8.5 kg; two experienced hypotension and one bradycardia. The AEs resolved shortly after the DEX discontinuation, and no harm was reported to the patients, nor was any further treatment needed. Eventually, 40 patients were analyzed in the interim analysis.

3.2 | Demographic, clinical, and sedation characteristics according to treatment group

Demographic, clinical, and sedation characteristics according to the intervention arm are reported in Tables 1 and 2. Patients receiving DEX had a significantly lower pediatric index of mortality 3 (PIM3) score at admission ($p = 0.028$). There were no other significant baseline differences between the two groups.

3.3 | DEX efficacy in reducing the prevalence of WS – primary outcome

The prevalence of opioid/benzodiazepine WS (defined as WAT-1 ≥3) did not significantly differ between the two treatment groups (14/18 [77.8%] patients in the DEX group vs 20/22 [90.9%] in the placebo group, $p = 0.381$). Considering a WAT-1 cut-off for WS definition equal to WAT-1 ≥5, 11/18 [61%] patients experienced WS in the DEX-group and 11/22 [50%] in the placebo-group ($p = 0.537$, CP = 0.63).

3.4 | DEX efficacy – secondary outcomes

The analysis of WAT-1 score trend over time using GLMM showed that WAT-1 score was significantly different in the two groups at time 0. In particular, the estimated mean WAT-1 score at time 0 was significantly lower in the DEX arm compared with the placebo arm (estimate −0.78, confidence interval (CI) −1.51–-0.05, $p = 0.037$) (Figure 3). However, the increase of WAT-1 score per unit of time (day) was significantly higher in the DEX arm compared with the placebo arm. This is true both when considering WAT-1 data in the first 3 days of weaning only (estimate 0.75, CI 0.26–1.23, $p = 0.002$) (Figure 3A), in the first 6 days only (estimate 0.18, CI 0.05–0.30, $p = 0.006$) (Figure 3B), and when considering all the WAT-1 timepoints (estimate 0.27, CI 0.07–0.47, $p = 0.009$) (Figure 3B). In this last model, predicted WAT-1 values decreased after day 6 in both arms, persisting higher in the DEX-group (Figure 3B). The number of opioid and benzodiazepine rescue doses, the length of benzodiazepines and opioid weaning, and the length of PICU-stay were not significantly different between the two groups (Table 2).

3.5 | DEX Safety

As reported above, three patients enrolled in the DEX-arm experienced significant hemodynamic AEs after the introduction of DEX and exited the study. Among patients who completed the study, four experienced bradycardia (≤20% to patient baseline values); all were enrolled in the DEX-group ($p = 0.033$). Overall, no AEs were reported among patients receiving placebo.

After the DEX/placebo weaning, five patients developed rebound signs such as tachycardia and hypertension; all had received DEX (5/18 [28%], Table 2). None of the patients developed signs compatible with opioid/benzodiazepine WS after the PICU discharge.

4 | DISCUSSION

In this RCT, we showed that a continuous infusion of DEX, started 24 h before opioid/benzodiazepine weaning and increased based on early detection of WS signs, was not able to significantly decrease the prevalence of WS in critically ill pediatric patients at high risk of WS (i.e., who received at least 5 days of opioid/benzodiazepine

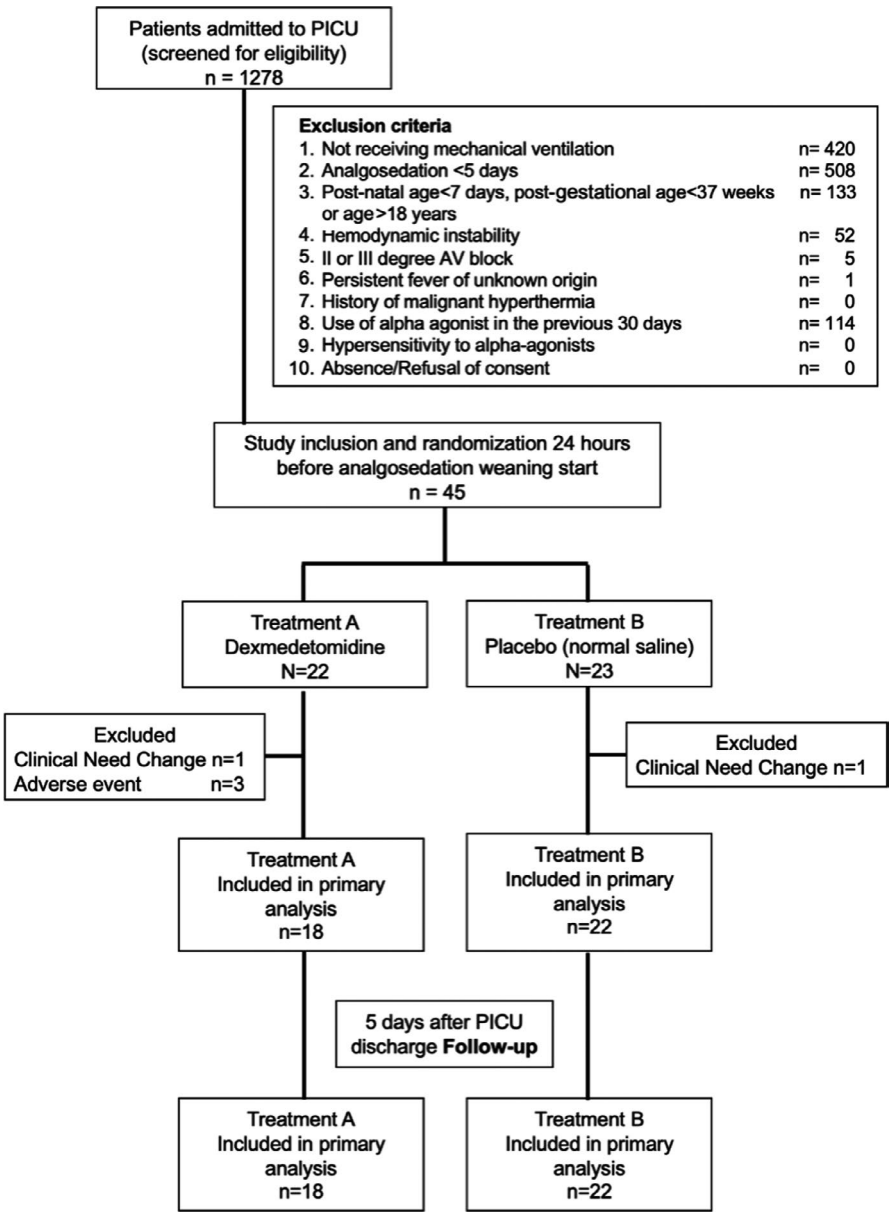


FIGURE 2 Study flow chart. Abbreviations: PICU, Pediatric Intensive Care Unit

infusions), compared to placebo. DEX has been confirmed to be safe; however, mild cases of bradycardia or hypotension may occur with need for DEX discontinuation.

WS secondary to analgosedation weaning is frequently observed in the PICU and associated with higher risk of adverse prognosis.[18] To date, limited strategies have been proven to be effective in preventing or managing WS occurrence. The most commonly used strategy is slowly tapering off the analgosedation infusion following a scheduled weaning protocol. However, this strategy alone is not always effective.[19] Multiple other efforts have been made to identify interventions able to reduce the prevalence of WS in the PICU, but the most effective is yet to be determined. Among them, DEX has been suggested to have a possible role both as a prophylaxis strategy and as a treatment of this complication.[20] The pharmacologic mechanism is hypothesized to be based on DEX's alpha-2-receptor agonism resulting in a synergic analgesic interaction with opioids, in addition to a concomitant sympathetic inhibition.[21] Two recent reviews, which summarized data from retrospective studies and case reports/series, illustrated the successful use of DEX for both prevention and treatment of WS.[11,12] However, a systematic review including 32 studies using DEX infusion in the PICU showed that only five studies reported the use of DEX as an adjuvant for weaning, and only two described its use for treatment of WS.[22] In a recent prospective multicenter study (PROSDEX) including 163 pediatric patients, DEX was confirmed to be used both for prevention of WS (12% of patients) and as an adjuvant for its treatment (15%). Interestingly, this study also showed that the WAT-1 score significantly decreased at 24 h of DEX infusion by a median of 2 points (interquartile range (IQR), 1–4), and the prevalence of WS decreased from 19% to 2% after start of DEX infusion ($p < 0.001$).[23] These promising results certainly encouraged the design of this randomized clinical trial in the attempt to add further supporting evidence to the current knowledge for the use of DEX as an adjunctive treatment for WS. However, it may be appropriate to specify that the outcome measures of the PROSDEX study were evaluated at a single 24-hour timepoint, whereas in our

TABLE 1 Demographic and clinical characteristics according to study arm

Variable	Treatment Placebo $N = 23$	Treatment DEX $N = 22$	Overall $N = 45$	p value
Age (months)	15.0 (2.6–27.1)	9.2 (4.5–25.9)	11.3 (5.5–26.7)	0.935
Weight (kg)	9.5 (4.35–12.5)	7.4 (3.93–10.8)	9.25 (6.25–11.15)	0.732
Gender (male)	14 (61)	15 (68)	29 (64)	0.758
Ethnicity				
Caucasian	17 (73.9)	18 (81.8)	35 (77.8)	0.361
Arabic	1 (4.3)	0 (0)	1 (2.2)	
African	4 (17.4)	3 (13.6)	7 (15.6)	
Asian	1 (4.3)	0 (0)	1 (2.2)	
Hispanic	0 (0)	1 (4.5)	1 (2.2)	
PIM3	0.017 (0.008–0.053)	0.009 (0.003–0.021)	0.011 (0.005–0.050)	0.028
Reason of PICU admission				
Respiratory failure	11 (47.8)	8 (36.4)	19 (42.2)	0.550
Surgery	6 (26.1)	4 (18.2)	10 (22.2)	0.722
Sepsis	0 (0)	1 (4.5)	1 (2.2)	1.000
Trauma	3 (13.0)	0 (0)	3 (6.7)	0.233
Burns	1 (4.3)	3 (13.6)	4 (8.9)	0.346
Neurological disease	0 (0.0)	2 (9.1)	2 (4.4)	0.233
Cardiac disease	2 (8.7)	3 (13.6)	5 (11.1)	0.665
Onco-hematological disease	0 (0.0)	1 (4.5)	1 (2.2)	1.000

Note: Data are reported as numbers (percentages) and median (I, III quartile).

Abbreviations: DEX, dexmedetomidine; PICU, Pediatric Intensive Care Unit; PIM3, pediatric index mortality score-3.

trial, this evaluation was undertaken until the end of weaning from the drugs as a continuous variable. Furthermore, PROSDEX was an observational study which collected data from a non-homogeneous population, and in which each participating center adopted use of DEX with different protocols and unpredictable dosages.

For the purpose of our study, the presence of WS was defined as at least one WAT-1 assessment ≥3. In fact, in the WAT-1 validation study, Franck et al. showed a high sensitivity and specificity of WAT-1 score ≥3 for WS detection.[15] In our analysis, the prevalence of WS did not significantly differ between patients treated with DEX compared to placebo. When allowing a more conservative definition of WS (i.e., WAT-1 ≥5) to avoid overestimation of the WS prevalence and underestimation of the DEX effect, the WS prevalence in the two groups did not significantly differ either, suggesting that DEX infusion, used as described above, is not particularly effective in reducing the prevalence of WS in pediatric patients. When analyzing the WAT-1 score over time by GLMM, we also showed that WAT-1 increased significantly more per unit of time in the group of patients receiving DEX compared to placebo. However, this analysis may be limited by the small sample size and by the consequent less conservative assumptions intrinsic to the model. Interestingly, the estimated mean WAT-1 score at time zero (i.e., the time of opioid/benzodiazepine weaning, after 24 h of DEX infusion) was significantly lower in the DEX-arm. This finding may be explained by an initial but only temporary efficacy of DEX that may be rapidly neutralized by the early onset of phenomena such as tachyphylaxis. Other authors had already hypothesized a mechanism of tolerance to DEX beyond the first 24 h of infusion.[24]

Multiple factors may have contributed to the missed effect of DEX in preventing WS in our trial. First, the analgosedation regimens before the enrollment were not standardized, and significant differences regarding the previously received sedation and analgesia may not have been captured well using the non-parametric analysis requested by the small sample size. Second, we chose to define WS as at least one record of WAT-1 score ≥3, following the most recognized cut-off by literature. Interestingly, testing the cut-off of WAT-1 ≥5 in order to be more conservative (i.e., do not overestimate the WS event and do not underestimate the DEX effect), allowed us to retrospectively calculate a CP of 0.63, suggesting that using a different WS definition may lead to identifying significant differences in WS prevalence in a similar trial with wider samples. Third, we chose to maintain a DEX medium-dose infusion for 24 h before weaning any opioid/benzodiazepine infusion; in the absence of recommendations of DEX use for WS prevention, we deliberately

TABLE 2 Analgesia and sedation characteristics before and during the weaning according to study arm

Variable	Treatment Placebo *N* = 22	Treatment DEX *N* = 18	*p* value
Patients receiving benzodiazepines (midazolam)	22 (100)	18 (100)	1.000
Length of benzodiazepines infusion before weaning (h)	210 (168.0–279.0)	183.5 (144.0–295.0)	0.399
Cumulative doses before weaning of intravenous benzodiazepines (mg/kg)	42 (23.0–71.3)	36.2 (25.0–43.5)	0.447
Maximum benzodiazepines dose (mg/kg/h)	0.25 (0.20–0.36)	0.23 (0.20–0.30)	0.711
Baseline midazolam dose at the start of weaning (mg/kg/h)	0.275 (0.140–0.390)	0.220 (0.162–0.300)	0.452
Patients receiving opioids[a]	22 (100)	17 (94.4)	0.450
Fentanyl	21 (95.5)	16 (94.1)	1.000
Morphine	3 (13.6)	5 (29.4)	0.261
Remifentanil	2 (9.1)	1 (5.9)	1.000
Length of opioids infusion before weaning (h)	189.5 (142.0–270.0)	168 (144.0–283.0)	0.854
Cumulative doses before weaning of intravenous opioids (μg/kg)[b]	404.3 (260.0–715.0)	346.9 (200.0–456.0)	0.166
Maximum opioids dose (μg/kg/h)[b]	3.00 (3.00–4.00)	2.5 (2.00–4.00)	0.109
Baseline opioids dose at the start of weaning (μg/kg/h)[b]	3.00 (2.00–3.25)	2.00 (2.00–3.20)	0.512
Total number of benzodiazepine rescue doses	10 (2.0)	14 (3.4)	0.212
Total cumulative doses of intravenous benzodiazepines (mg/kg)	60.3 (36.2–99.4)	57.2 (27.7–93.9)	0.870
Length of intravenous benzodiazepines weaning (h)	126 (96.0–156.0)	108 (96.0–132.0)	0.374
Length of benzodiazepines weaning including oral therapy (days)	9.5 (6.0–16.0)	9.0 (5.0–18.0)	0.957
Total number of opioid rescue doses	11 (2.1)	10 (2.4)	0.826
Total cumulative doses of intravenous opioids (μg/kg)[b]	630 (492.0–893.0)	490 (378.4–688.0)	0.103
Length of intravenous opioids weaning (h)	132 (96.0–158.0)	108 (96.0–144.0)	0.353
Length of opioids weaning including oral therapy (days)	8.5 (6.0–17.0)	11 (5.0–15.0)	0.853
Total length of DEX/placebo infusion (h)	192 (180–240)	174 (156–264)	0.286
Length of DEX/placebo weaning (h)	29.5 (22.0–48.0)	24.0 (16.0–66.0)	0.429
DEX rebound/withdrawal symptoms after DEX/placebo interruption			
Tachycardia	0 (0)	2 (11.1)	0.196
Hypertension	0 (0)	2 (11.1)	0.196
Agitation	0 (0)	1 (5.6)	0.450
Length of PICU stay (days)	20 (16–24)	19 (13–25)	0.663

Note: Data are reported as numbers (percentages) and median (I, III quartile).

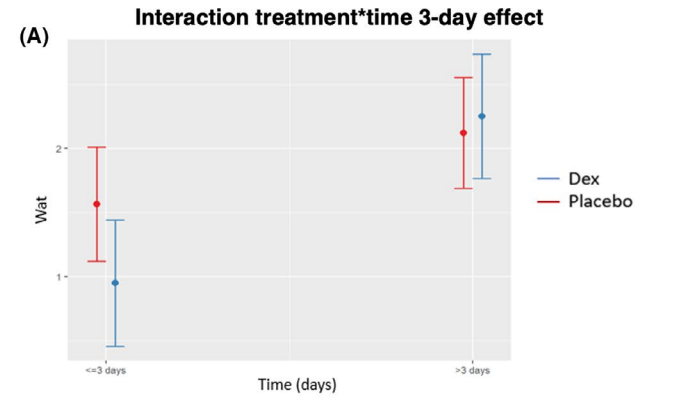
Abbreviations: DEX, dexmedetomidine; PICU, Pediatric Intensive Care Unit.

aPatients could receive more than one opioid during their analgosedative management.

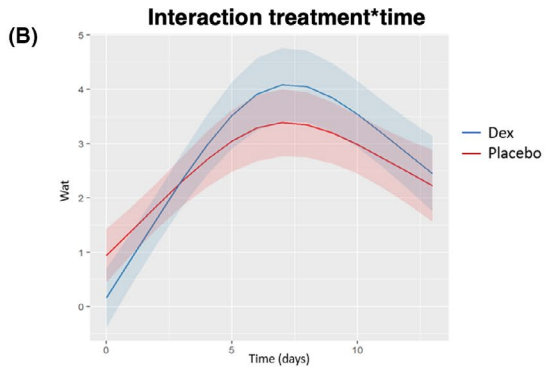
bCumulative doses for opioids were calculated as fentanyl equivalents in μg/kg. Opioids include morphine (1), fentanyl (0.01), and remifentanil (0.15).

decided on this infusion regimen, which may have induced tachyphylaxis and the subsequent ineffectiveness of DEX. Finally, we chose to increase the DEX infusion rate every time the WAT-1 became positive. It may be argued that this could be considered as treatment rather than prophylaxis, and that once the WS has manifested, a small increase in DEX infusion rate may not be effective and may not even be necessary. In light of these limits, it might be reasonable to try to reformulate the interventional trial design before concluding that DEX is not effective to prevent opioid/benzodiazepine WS. Different DEX dosages or different modalities of use could be considered, such as starting the weaning earlier or increasing DEX dosages in the early phases of the weaning process regardless of the WAT-1 value.

Another important aspect regards any safety concerns with the use of DEX. Overall, there were no AEs requiring intervention other than the DEX discontinuation, and this is consistent with what was described in previous studies.[23] However, less severe events, mostly bradycardia and/or hypotension, were recorded among patients in the DEX arm which led to DEX discontinuation and drop-out from the study. Thus, our study confirms that DEX infusion could be considered overall relatively safe; however, in some patients, there could be a particularly intense hemodynamic response, with the possible need to suspend the infusion.



Predictors	Estimates	CI	p
(Intercept)	1.57	1.12 – 2.01	<0.001
Treatment Dex	-0.62	-1.28 – 0.05	0.069
time [≤3 days]	0.56	0.24 – 0.88	0.001
Treatment Dex* time [≤3 days]	0.75	0.26 – 1.23	0.002



Global Effects

Predictors	Estimates	CI	p
(Intercept)	0.94	0.45 – 1.43	<0.001
Treatment Dex	-0.78	-1.51 – -0.05	0.037
Time	0.45	0.32 – 0.59	<0.001
Treatment Dex* Time	0.27	0.07 – 0.47	0.009

Time≤6 days effects

Predictors	Estimates	CI	p
(Intercept)	1.16	0.70 – 1.61	<0.001
Treatment Dex	-0.71	-1.39 – -0.04	0.039
Time	0.24	0.16 – 0.33	<0.001
Treatment Dex* Time	0.18	0.05 – 0.30	0.006

Time>6 days effects

Predictors	Estimates	CI	p
(Intercept)	3.66	1.69 – 5.62	<0.001
Treatment Dex	1.74	-0.99 – 4.48	0.212
Time	-0.21	-0.44 – 0.03	0.082
Treatment Dex* Time	-0.16	-0.47 – 0.15	0.313

FIGURE 3 Modeling of WAT-1 score over time by Generalized Linear Mixed Models according to study arm. The estimated mean WAT-1 value with 95% Confidence Intervals and *p*-value have been computed. Plots report the estimated WAT-1 over time with the 95% confidence bounds. Non-linear effects were modeled by Restricted Cubic Spline method. Abbreviations: Dex, dexmedetomidine; Wat, withdrawal assessment tool-1

4.1 | Strengths and limitations

To our knowledge, this study is the first RCT to investigate the use of DEX infusion for the prevention of WS in pediatric patients. Main strengths include the systematic use of the validated tool WAT-1, the multicenter design, and the optimal adherence to the protocol with no lost to follow-up or loss of data. However, as partially mentioned above, some limitations have to be acknowledged. First, the results are limited by the small sample size, even though this size corresponded to that planned for the interim analysis. The lack of a standardized analgosedation protocol pre-enrollment may have influenced the outcomes. Even if not planned, our study enrolled mainly infants and toddlers, rather than older children, with risk of a significant selection bias. Despite its limitations, we believe that this trial could represent a pivotal step in evaluating the role of DEX for WS in critically ill children and strongly suggests the need for additional dedicated research projects in the field.

5 | CONCLUSIONS

Our RCT showed that a continuous infusion of DEX, started 24 h before the weaning of opioid/benzodiazepine and increased based on early detection of WS signs, was not able to significantly modify the prevalence of WS in critically ill pediatric patients who received at least 5 days of opioid/benzodiazepines, compared to placebo. These results may be limited by sample size and by the protocol design. Future efforts should be made to confirm or reject these results, and for defining the role of DEX in WS prevention and treatment.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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