Efficacy and safety of Dexmedetomidine for prevention of withdrawal syndrome in Pediatric Intensive Care Unit Protocol for a prospective, multicenter, randomized, double blind, placebo-controlled, non-profit clinical trial (TIP-15-01)

CURRENT STATUS: ACCEPTED

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Abstract

Background: Prolonged treatment with analgesic and sedative drugs in Pediatric Intensive Care Unit (PICU) may lead to undesirable effects as dependence and tolerance. Moreover, during the analgosedation weaning patients may develop clinical signs of withdrawal, known as withdrawal syndrome (WS). Some studies indicated that dexmedetomidine, a selective α2-adrenoceptors agonist, may be useful to prevent WS, but no clear evidences still support this data. Aims of the present study are to evaluate the efficacy of dexmedetomidine in reducing the occurrence of WS during the analgosedation weaning, to evaluate its safety, to identify its optimal dose-range and to quantify its ability in reducing time of weaning, time of mechanical ventilation and PICU-stay. Methods: We will perform a prospective, multicenter, randomized, double-blind, placebo-controlled study. Patients meeting the inclusion criteria will be randomly assigned to treatment A (dexmedetomidine) or treatment B (placebo). Treatments will be started 24 hours before the analgosedation-weaning and will be continued throughout the whole weaning time. Efficacy of treatments will be evaluated by monitoring the signs of WS using the withdrawal assessment tool version 1 score (WAT-1). If WAT-1 score is ≥3, dexmedetomidine/placebo-dose will be increased following a defined protocol. Thus, efficacy will be compared between treatment groups. Safety will be assessed collecting any potentially-related adverse event. Clinical or sedation characteristics will be analyzed to assess any significant association with outcome measures. The sample size assuring a power of 95% is 80 patients for each group (N total=160 patients). The study was approved by the Ethics Committee of the University-Hospital S.Orsola-Malpighi of Bologna on 22 March 2017. Discussion: The present trial will allow to clearly assess the efficacy of dexmedetomidine in reducing the occurrence of WS during the weaning of analgosedation drugs. In addition, the study will provide a unique insight into the safety profile of dexmedetomidine. Trial registration: ClinicalTrials.gov ID NCT03645603, registered on 24 August 2018, https://clinicaltrials.gov/ct2/show/NCT03645603. Retrospectively registered on EudraCT with ID 2015-002114-80, registered on 2 Jan 2019.

Background

Analgesia and sedation are essential treatments required by the majority of children admitted to the
Pediatric Intensive Care Unit (PICU). In addition to their favorable effects, a prolonged exposure to analgosedation drugs may lead to undesirable effects, such as dependence, tolerance and withdrawal syndrome (WS) [1,2,3]. The presence of WS causes intense suffering and increases morbidity and length of PICU-stay [3]. For this reason, several studies in the last decades has been designed to identify WS risk factors and an intense effort has been made to find any possible prevention strategy to avoid the onset of WS [4]. Despite that, no clear strategy has been identified so far and the prevention of WS still remain a challenge for the pediatric intensivist.

Recently, some studies indicated that dexmedetomidine, a selective α2-adrenoeceptors agonist, may be useful to prevent WS [5,6] but, up to now, no clear evidence supports its role in WS prevention. We conceived a prospective randomized controlled trial with the main aim to evaluate the efficacy of Dexmedetomine in reducing the incidence of WS during the weaning of conventional analgesic and sedative drugs. Secondary objectives of our study are (1) to evaluate the safety of dexmedetomidine during the weaning of analgosedation drugs, (2) to define the ability of dexmedetomidine in reducing the duration of the analgosedation weaning, (3) to evaluate its ability in reducing the length of mechanical ventilation and (4) the PICU-stay, (5) to compare the efficacy of dexmedetomidine among pediatric age-groups, gender, race, clinical severity and length of analgosedation treatment. Finally, (6) to evaluate the most effective dose-range of dexmedetomidine in reducing the occurrence of WS.

Methods

Design

TIP-15-01 is a prospective, multicenter, randomised, double blind, placebo-controlled, non-profit, superiority clinical trial with two-parallel groups. The study will be conducted in adherence to the principles of the World Medical Association’s Declaration of Helsinki. The Study Protocol Final Version 2.0 (18 September 2016) was approved by the Ethics Committee of the Coordinating Center (University-Hospital S.Orsola-Malpighi of Bologna) on 22 March 2017. All centers received approval from the local Ethical Committee. The study was authorized by the Italian Medicines Agency and registered in the National Monitoring Center for Clinical Trial (OsSC) and successively in Eudra CT Register (Identification Number 2015-002114-80). In addition, the study was prospectively registered
on the ClinicalTrial.gov Registry (registration date 24 August 2018) with the Identification Number NCT03645603. The protocol has been designed following the SPIRIT international guidelines: Figure 1 shows the SPIRIT-schedule of enrolment, interventions and assessments and a populated SPIRIT Checklist is attached as Additional File 1.

| STUDY PERIOD | ENROLMENT | Allocation | Post-allocation | Close-out | TIMEPOINT |
|--------------|-----------|------------|-----------------|-----------|-----------|
| Enrolment    | Eligibility screen | X | 0 | 24h before start of AS weaning | -t1 |
| Allocation   | Informed consent | X | 24h before start of AS weaning | during AS weaning | 0 |
| INTERVENTIONS: | Allocation | X | up to 72h after stop AS | up to 72h after stop AS | 24h before start of AS weaning |
| ASSESSMENTS: | Baseline variables | X | X | 5 days after PICU discharge | 5 days after PICU discharge |
| WAT-1 every 12 h | X | X | X | X | X |
| Hemodynamic parameters | X | X | X | X | X |
| AR, AE, SUSARs | X | X | X | X | X |
| Follow-up variables | X | X | X | X | X |

Figure 1. SPIRIT figure: Schedule of enrolment, interventions, and assessments of the TIP-15-01 trial.

Legend: AE: Adverse Event; AR: Adverse Reactions; AS: Analgesedation; SUSARs: Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions; WAT-1: Withdrawal Assessment Tool version 1.

Setting

The study will involve three PICUs belonging to three tertiary-care pediatric academic centers.
Study population

The study population will involve patients admitted to PICU who meet the following criteria (Figure 2).

**Inclusion Criteria:** (1) age from 0 to 18 years, (2) post-natal age ≥ 7 days and post-menstrual age (gestational age at birth (weeks) plus weeks since birth) ≥ 37 weeks, (3) having received continuous intravenous analgesedation with opioids and/or benzodiazepines for at least five days, (4) having required invasive or non-invasive mechanical ventilation, (5) presence of clinical conditions that allow the treating physician to start the analgesation weaning, including absence of signs and symptoms of WS, (6) parents’ written consent obtained.

**Exclusion Criteria:** (1) presence of hemodynamic instability according to the treating physician judgement; (2) receiving inotropic or antihypertensive treatments (β-blockers, calcium antagonists, ACE inhibitors, digoxin, nicardipine, nitroglycerin), (3) presence of II or III degree cardiac atrio-ventricular (AV) block; (4) known or suspected hypersensitivity to alpha-agonists; (5) presence of persistent unknown-origin fever or history of malignant hyperthermia; (6) use of alpha-agonist (clonidine or dexmedetomidine) in the 30 days preceding the study enrolment.

Definitions

**Withdrawal syndrome:** WS is defined as iatrogenic clinical syndrome that manifests when the administration of a sedative or analgesic agent is abruptly discontinued or too rapidly weaned in a patient who is physically tolerant [2].

**Withdrawal Assessment Tool version 1 (WAT-1):** WAT-1 is a validated assessment tool for monitoring withdrawal symptoms in pediatric patients. This twice-daily assessment consists of 11 items, determined by the following components: a review of the patient's record for the past 12 hours, a direct observation of the patient for 2 minutes, a patient assessment using a progressive stimulus and an assessment of post-stimulus recovery [7]. The score ranges from 0 to 12 and a score ≥3 indicates the presence of signs or symptoms of WS. The severity of WS is grading from mild to severe in proportion to the value of the score.
Recruitment and Consent

Comprehensive information will be provided by each Center Principal Investigator to parents of children potentially involved. A detailed information sheet has been designed to support the oral communication. Written informed consent will be obtained from both parents for each involved child. Even when appropriate for age, a child’s consent will be not needed because of the sedation status. A guarantee of optimal children care will be assured independently of the study involvement. Consent refusal will be recorded.

Randomisation

Each patient will be randomly assigned to one of the two treatment groups: treatment-A group (receiving dexmedetomidine) or treatment-B group (receiving placebo). An identification code will be individually assigned to each enrolled patient. The Investigational Drug Service of the Coordinating Center will generate a single randomisation list for all centers. This confidential document will be available only to the non-blinded staff involved, who will carry out the preparation of the treatments. Thus, the allocation sequence and the treatment administration will be unknown for the blinded researchers, including the study Principal Investigator. During the study, two sealed copies of the randomisation list that clearly show the treatment attributed to the patient will be available for emergencies. A sealed list will be kept in the archive of the Investigational Drug Service of the Coordinating Centers and the other in the archive of each Principal Investigator. If opening is needed, the Investigator will have to describe the reason, to register the date/time and to immediately notify the Project Principal Investigator.

Interventions

Twenty-four hours before the start of the analgosedation weaning, an intravenous infusion of dexmedetomidine or placebo (i.e. normal saline) will be started according to the following schedule (Figure 2). The starting dose will be 0.4 mcg/kg/h. No loading dose will be administered. If the infusion will be well-tolerated (i.e. without the occurrence of adverse effects), the dose will be increased of 0.2 mcg/kg/h per hour up to 0.8 mcg/kg/h. Given the pharmacological peculiarities of the neonatal period [8], newborns will receive a starting dose of 0.2 mcg/kg/h, which will be increased of 0.1mcg/Kg/h up
to 0.4 mcg/Kg/h. At 24 hours of dexmedetomidine infusion, the analgosedation weaning process will be started, consisting in a 10% reduction of one of the drugs every 12 hours. If requested, a switch from opioid and/or benzodiazepine to an equipotent drug of the same pharmacological class but longer half-life will be allowed (including enteral methadone, morphine, lorazepam). The switch should be aimed to facilitate patient’s management. In the same way as iv drugs, enteral drugs will be weaned with 10% reduction every 12 hours.

WAT-1 scale will be administered every 12 hours from the starting of the treatment infusion. If WS will be diagnosed, clinician will administer a rescue dose of the using opioid and/or benzodiazepine, repeatable until resolution of the crisis, and will increase the dexmedetomidine/placebo dose by 0.2 mcg/kg/h (0.1 mcg/Kg/h in neonates). If the following WAT-1 score shows a decrease by at least 1 point compared with the previous one, the weaning program will be restarted (by 10% of reduction) and the current dexmedetomidine/placebo dosage will be maintained. If the WS symptoms persist, dexmedetomidine/placebo will be increased by 0.2 mcg/kg/h (0.1 mcg/Kg/h in neonates) every 12 hours according to the WS score, up to a maximum of 1.6 mcg/Kg/h (0.8 mcg/kg/h in neonates).

Once the analgosedation weaning will be completed, dexmedetomidine will be weaned or discontinued. A gradual reduction of the dexmedetomidine dose is strongly recommended to prevent the risk of dexmedetomidine withdrawal [9,10], but it is not mandatory. Since the analysis of dexmedetomidine weaning is not a specific aim of the present study, no specific protocol will be recommended. Time and modality of dexmedetomidine weaning will be recorded.

A follow-up visit will be performed at five days after PICU discharge, with the aim to collect the following data: (1) actual duration of the analgosedation weaning when longer than 5 days (days), (2) values of WAT-1 scores collected every 12 hours up to 72 hours after the analgosedation discontinuation, (3) length of dexmedetomidine weaning (hours), (4) occurrence of signs and symptoms of dexmedetomidine withdrawal, including values of WAT-1 scores until 72 hours after treatment discontinuation.

Outcome measures

Primary outcome measure
The primary outcome measure of our study is the treatment efficacy in WS prevention. Treatment will be defined effective if: (1) the WAT-1 score will be maintained <3 during the whole analgosedation weaning and up to 72 hours after, (2) a positive WAT-1 score (≥3) will respond to the increase of the treatment dosage (dexmedetomidine/placebo) with a consequent decrease of at least 1 point.

Efficacy will be compared between the two treatment groups. Then, efficacy will be compared also among groups defined by clinical or sedation characteristics, such as age, sex, race, severity of illness estimated also with the Pediatric Index of Mortality score (PIM3) and length of analgosedation treatment. Finally, the most effective dose-range will be identified.

Secondary outcome measures

Treatment safety

The safety of the treatment will be assessed: (1) with a strict monitoring of hemodynamic parameters (heart rate, systolic and diastolic blood pressure) which are considered altered if their value will differ more than 20% comparing with the patient’s baseline values, (2) collecting every potentially-related Adverse Reactions (AR), Adverse Events (AE), Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions (SUSARs).

Secondary outcome measures related to Efficacy

Secondary outcome measures evaluated to confirm the efficacy of the treatment will be: (1) number of rescue doses required for WS symptoms; (2) number of temporary discontinuations of the analgosedation weaning due to presence of WS, (3) duration of analgosedation weaning (days), (4) length of mechanical ventilation (days); (5) PICU length of stay (days).

Data collection and management

Blinded investigators and staff will collect data by means of a standardized paper case report form (CRF). Paper CRFs will be stored in accordance with national regulations. Paper CRFs will have an identifiable patient code in order to allow a clinical follow-up and a data monitoring by national coordinators or regulatory committees. Investigators will transcribe each patient’s data into an electronic CRF using the identification code. No patients’ identifiable data will be directly accessible from the electronic CRF. Data recorded on each CRF will be entered in a dedicated database, checked
and subsequently processed.

Sample size
A recent multicenter national study reported a WS incidence of 64.6% among PICU patients receiving more than 5 days of analgosedation with opioids and/or benzodiazepines [11]. The sample size has been calculated considering these incidence data and estimating that dexmedetomidine could reduce the WS incidence by 29%. Assuming a confidence interval of 95% and a statistical power of 95%, a number of 77 patients have been calculated for each group, with a total of 154 patients. To ensure a correct balancing of the randomization, 160 patients will be enrolled.

Statistical analysis
The population who will complete the study without any major protocol violations will be analysed in relation to the outcome measures. An analytical detailed list of patients who will discontinue the study for AR, AE or SUSARs and related reasons of discontinuation will be provided.
A descriptive analysis will be performed using frequencies and percentage for categorical variables, means and standard deviation for variables with Gaussian distribution and median and inter-quartile range for non-parametric variables. A two-sided p-value < 0.05 will indicate statistical significance.
A significant difference in efficacy between the two treatment groups will be tested by means of Pearson’s 2 test (or Fisher’s Exact test if subgroups will be <5 patients). Differences among variables and main or secondary outcome measures will be assessed using Pearson’s 2 test or Fisher’s Exact test for qualitative variables, as well as with t-test for variable with normal distribution and U-Mann-Whitney test for non-parametric variables. Variation of WAT-1 scores during time will be analysed with paired-sample t-test or Wilcoxon test depending on the variable distribution. Comparison among multiple groups, such as differences among centers, will be assessed by means of ANOVA test or Kruskal Wallish test depending on the variable distribution.
A multivariate logistic regression model including all the variables considered related with the outcome measures will be applied to identify independent risk and protective factors associated with each outcome measure.

Trial status
The TIP-15-01 trial (Study Protocol Final Version 2.0, approved on 18 September 2016) is currently ongoing. All centers are actively recruiting patients. From the beginning of the enrolment (30 August 2018) to date (9 February 2019), 26 of 160 patients have been recruited. The period for the whole population enrolment has been estimated as a three-year period (estimated end-of-enrolment date: August 2021).

**Discussion**

Prolonged exposure to analgosedation may lead to undesirable effects, such as dependence, tolerance and withdrawal syndrome (WS) [1,2,3]. WS is a clinical syndrome occurring after discontinuation or during the weaning of analgosedation drugs and represents one of the most important cause of morbidity in patients under prolonged-sedation in PICU. Its incidence among PICU-patients has been described between 17 and 57%, up to 64.6% among patients undergoing five or more days of treatment [11]. The syndrome is characterized by central nervous system excitement, gastrointestinal disturbance and sympathetic system activation. Typical symptoms are tremors, agitation, sleeplessness, inconsolable crying, sweating, yawning, sneezing and diarrhoea or vomiting for opioid drugs. To estimate the WS severity, multiple clinical scores have been described and two of them have been recently validated for the pediatric age: the Withdrawal Assessment Tool version 1 (WAT-1) and the Sophia Observational withdrawal Symptoms-scale (SOS) [7,12]. Since the presence of WS causes intense suffering and increases morbidity and length of stay, several studies have been conducted so far to identify the main risk factors. The cumulative dose of the analgosedation drug and the duration of treatment have been described as main factors associated with the onset of WS, as well as the rapid dosage reduction and the abrupt discontinuation of the treatment. [4]. Thus, WS prevention strategies have been addressed both to restriction of drug exposure and to tapering of the infusion. A strategy of drug-switch has been also proposed, replacing the using drug with another equipotent drug with longer half-life. Although no drugs seem more effective than others, methadone is the most commonly prescribed in a contest of switching strategy [13]. However, the efficacy of these strategies is unclear and the prevention of WS is still a real challenge for the paediatric intensivist.
In the past decades, some studies have suggested that dexmedetomidine, a selective α2-agonist, may be useful to prevent WS during the weaning of analgosedation drugs [5,6,14-17]. Binding the α2-receptor, dexmedetomidine is able to block the release of noradrenaline in the locus coeruleus and to induce a sedative and anxiolytic effect [1]. In addition, it is also able to block the substance-P release in the dorsal horns of the spinal cord, mediating a mild analgesic effect [18-21]. Finally, the sympathetic inhibition is also responsible for the most common adverse effects, such as hypotension and bradycardia, usually easily reversible with dose reduction [22,23].

The concept that dexmedetomidine could have a potentiality in WS-management and prevention originated from the knowledge of other α2-receptor agonists, i.e. clonidine and lofexidine, used in adult population as adjuvants of WS-treatment [5, 24]. In fact, the ability of α2-agonists to interact with the sympathetic system represents the pharmacological rationale for their use as adjuvant-drug for the management of WS, which is characterized by sympathetic activation [24]. The interaction between Dexmedetomidine and opioids has been first described in murine models treated with morphine prolonged-infusions and inducted to present WS [25]. The authors described that dexmedetomidine and opioid seem to have a reciprocal adjuvant effect to induce both analgesia and hypnosis. During opioid-WS, dexmedetomidine maintains its hypnotic effect even if its analgesic effect and the morphine-reciprocal effect decrease [25]. Despite these pre-clinical results, studies on dexmedetomidine for prevention of withdrawal syndrome have been limited to case report or small sample-size studies [14-17]. Also, its clinical use in pediatrics has been limited by its off-label status and only few high-evidence studies on prolonged-sedation are reported in literature [26].

The TIP-15-01 trial will aim to systematically analyse the efficacy of dexmedetomidine for prevention of WS in pediatric patients receiving prolonged analgosedation treatment. Its multicenter randomized controlled design will allow to clearly assess this research question with high level of evidence.

Moreover, the systematic evaluation of WS by means of a standardized score validated for pediatric age, i.e. the Withdrawal Assessment Tool version 1 (WAT-1), assures precision in the WS registration and makes stronger the validity of the study, as well as its reproducibility. TIP-15-01 is also feasible: the treatment (dexmedetomidine) is still available in most of the tertiary-care pediatric centers in
Europe and the resources requested for the implementation of the study are easily accessible. In case of proven efficacy of dexmedetomidine, the dexmedetomidine-arm of TIP-15-01 could be translated in a successful WS-prevention protocol, offering a real opportunity to adequately approach one of the biggest challenges on prolonged sedation in PICU. In addition, the TIP-15-01 study will measure if the use of dexmedetomidine could reduce the duration of conventional analgosedation, mechanical ventilation and PICU-stay. If any of these reductions is confirmed, TIP-15-01 could have also an impact in the PICU-resources management. Finally, TIP-15-01 will systematically evaluate any kind of dexmedetomidine-related adverse events, particularly the hemodynamic ones, providing a unique insight into the safety profile of this emergent drug.

Declarations

Ethics and consent to participate

The Study Protocol Final Version 2.0 (registered on 18 September 2016) was approved by the Ethics Committee of University-Hospital S.Orsola-Malpighi of Bologna on 22 March 2017. All centers approved the protocol. The study was also authorized by the Italian Medicines Agency National Authority. Written informed consent will be obtained from both parents of each involved child.

Consent for publication

Not applicable.

Availability of data and materials

The Principal investigator (MCM) and the authors will have full access to the final dataset data during the analysis. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Orion Pharma assured the liability insurance of the study (total amount of € 10.758). The supporter had no role in study design, decision to publish and preparation of the manuscript and will have no access or role in data collection and analysis. The authors have not received any personal funding or compensation for the research. Therefore, the authors did not have any personal interest to declare.

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Authors’ contributions

All authors contributed to the intellectual content of the protocol. MCM, GC, AA, FC conceptualized the study design, wrote the first study protocol and ensured ethical funding. FS and MD contributed to the manuscript writing and to define the statistical analysis plan. MFC, FV, MTC, MP, AM and AP contributed to the management of the study protocol in every center. All authors reviewed and approved the final version of the manuscript.

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List Of Abbreviations

AE: Adverse Events; AR: Adverse Reactions; AV: atrio-ventricular; CRF: Case Report Form; PICU: Pediatric Intensive Care Unit; PIM3: Pediatric Index of Mortality score; SUSAR: Suspected Unexpected Serious Adverse Reaction; WAT-1: Withdrawal Assessment Tool Version 1; SOS: Sophia Observational withdrawal Symptoms-scale; WS: Withdrawal Syndrome.

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Figures

Figure 1

SPIRIT figure. Schedule of enrolment, interventions, and assessments of the TIP-15-01 trial.

AE: Adverse Event; AR: Adverse Reactions; AS: Analgosedation; SUSARs: Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions; WAT-1: Withdrawal Assessment Tool version 1.

Figure 2

TIP-15-01 Study Protocol Flow Chart.

Legend: AV: Atrio-Ventricular; iv: intravenous; PICU: Pediatric Intensive Care Unit; WAT-1: Withdrawal Syndrome Assessment Tool-1; WS: Withdrawal Syndrome.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

Trials_SPIRIT_Checklist.pdf