PROTOCOLIZED SEDATION UTILIZING THE COMFORT –B SCALE VERSUS NON-PROTOCOL-DIRECTED SEDATION IN MECHANICALLY VENTILATED CHILDREN – A RANDOMIZED CONTROL TRIAL

THESIS

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DOCTOR OF MEDICINE (MD)

(PEDIATRICS)

MAY, 2022 **DR. PUJITHA VALLABHANENI**

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DECLARATION

I declare that the thesis titled **'Protocolized sedation utilizing the COMFORT –B scale versus non-protocol-directed sedation in mechanically ventilated children – a randomized control trial'** embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled **'Protocolized sedation utilizing the COMFORT –B scale versus non-protocol-directed sedation in mechanically ventilated children – a randomized control trial'** is the bonafide work of **Dr Pujitha Vallabhaneni** carried out under our guidance and supervision, in the Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur.

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LIST OF ABBREVATIONS

ARDS	:Acute Respiratory Distress Syndrome
BIS	:Bispectral Index
BP	:Blood Pressure
CI	:Confidence Interval
CLABSI	:Central line associated Blood Stream Infection
COMFORT B scale	:Comfort Behavioural Scale
DSI	:Daily Sedation Interruption
FLACC	:Face legs activity cry consolability scale
HFO	:High Frequency Oscillation
HR	:Heart Rate
IQR	:Interquartile range
ITT	:Intention to treat
MV	:Mechanical Ventilation
NISS	:Nurse Interpretation of Sedation Score
NMB	:Neuromuscular Blocker
NPS	:Non Protocolised sedation
LOS	:Length of Stay

pASP	:Pediatric Analgesia and Sedation Protocol
PELOD	:Pediatric Logistic Organ Dysfunction score
PENN scale	:Penn State Children's hospital sedation algorithm
PICU	:Pediatric Intensive Care Unit
PIM 3	:Pediatric Index of Mortality 3
PMODS	:Pediatric Multiple Organ Dysfunction Score
PRISM 3	:Pediatric Risk of Mortality 3
PS	:Protocolised sedation
RASS	:Richmond Agitation Sedation Scale
RCT	:Randomised control trial
RESTORE	:Randomized Evaluation of Sedation Titration for Respiratory Failure
RR	:Respiratory Rate
SBS	:State Behavioural Scale
SD	:Standard deviation
SOS	:Sophia Observation withdrawal Symptoms score
TOF	:Tetralogy of Fallot
VAP	:Ventilator Associated Pneumonia

VAS	:Visual Analogue Scale
WAT 1	:Withdrawal Assessment Tool 1

SUMMARY

Background:

The goal of sedation is safe and effective control of pain, anxiety and motion to allow a necessary procedure to be performed and to provide appropriate amnesia and decreased awareness in ventilated children. Objective assessment of sedation can be done with the aid of various sedation scales. Only two RCTs were found till date which used protocolized sedation with the aid of Comfort scale and State Behavioural Scale respectively for protocolized sedation and were found to have conflicting impact on outcome of the mechanically ventilated children admitted in PICU.

Objectives:

The primary aim of the study was to determine the effect of protocolized sedation using comfort B scale on the duration of mechanical ventilation.

The secondary objectives were to assess the outcome of protocolized sedation in the form of PICU LOS, hospital LOS, dose and duration of exposure of sedative agents and sedation related adverse events.

Methods:

Children between 1 month to 18 years who were admitted to PICU and required mechanical ventilation for more than 24 hours and fulfilling the eligibility criteria were enrolled in the study. Participants were randomised into intervention and control groups using variable block randomisation. Protocolized sedation was introduced in the intervention group along with the assessment of COMFORT B scale every 4^{th} hourly for titration of sedation. Following this, data regarding the outcome was collected.

Results:

We enrolled 80 patients into the study of which 40 were randomized into protocolized sedation and 40 were randomized into non protocolized sedation group. Intervention was discontinued in 6 patients in view of high sedation requirement but all 80 were analysed as per Intention to treat. The mean age of our study population was 2 years (IQR 0.8, 10.75). We found 62.5% male (n = 25) and 67.5% male (n = 27) in PS and NPS group respectively. Median duration of mechanical ventilation was found to be decreased in PS group (3.5 days; IQR 3, 7) in comparison to NPS group (8.5 days; IQR 4.25, 13.75; P = 0.008). Median duration of PICU stay was found to be significantly decreased in PS group (6.5 days; IQR 3,11.5 in PS group and 10 days; IQR 6.25, 22.5 in the control group; P=0.002). Both median duration of study period with pain score < 4 and pain score ≥ 4 were found to be decreased in PS group. (Pain score <4: 3 days, IQR 2, 7.75 in PS and 8 days, IQR 3, 16.5 in NPS group; P = 0.02; Pain score ≥ 4: 0.48 days ± 1.45 SD in PS group and 1.9 days ± 3.84 SD in NPS; P = 0.007). The incidence of ventilator associated pneumonia (VAP) was found to be significantly decreased in PS group (5%; n = 2 in PS group and 42.5%; n = 17 in NPS group; P = <0.001). There was statistically significant increased mean incidence of self extubation in NPS group (mean = 0.25 ± 0.49 SD) in comparison to PS group (mean 0.025 ± 0.16 SD; P = 0.007). Post extubation stridor was present in 2.5% (n = 1) in PS group in comparison to 20% (n = 8) in NPS group (P = 0.02). The mean duration with WAT 1 score ≥ 3 was found to be significantly more in the NPS group (mean 11.04 ± 19.44 hours in NPS; mean 0.96 ± 4.8 hours in PS; P = 0.02). Mean peak WAT 1 tool score was found to be higher in NPS group (1.23 ± 1.42 SD in NPS; 0.16 ± 0.62 SD in PS; P <0.001). The cumulative dose and duration of exposure of fentanyl in PS group was significantly lower than NPS group (120μ/kg; IQR – 62.88, 279.12 in PS; 320.4μg/kg; IQR 110.88, 851.52 in NPS; P = 0.007 and 4 days; IQR 2.25, 7.75; in PS and 8 days; IQR 4, 17.5 in NPS group P = 0.009). The median dose and cumulative dose of midazolam used was found to be decreased

in PS group (median dose 0.93 mcg/kg/min IQR - 0, 1.29 in PS; 1.1 mcg/kg/min, IQR - 0.87, 2.22 in NPS; P = 0.003; cumulative dose 4.32mg/kg; IQR 0, 9.17 in PS; 8.93 mg/kg; IQR 1.44, 36 in NPS; P = 0.005). The median number of sedative classes used in PS group was 2.15 (IQR 1, 3) which was significantly less than NPS group (2.58 classes IQR – 2, 3; P = 0.03).

Conclusion:

We found a decrease in MV duration, PICU LOS, sedation related adverse events such as incidence of VAP, incidence of accidental self extubation, post extubation stridor, withdrawal score and dose and duration of sedative agents with the use of protocolized sedation using COMFORT B scale.

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INTRODUCTION:

The goal of sedation is safe and effective control of pain, anxiety and motion to allow a necessary procedure to be performed and to provide appropriate amnesia and decreased awareness. Ensuring safety and comfort of critically ill children is integral to practice of pediatric critical care. Excessive sedation predisposes the patient to increased incidence of immobility related pressure ulcers, increased opioid tolerance, increased withdrawal symptoms, and increased length of hospital stay (LOS) (1–3). Increased usage of opioids and benzodiazepines will impair neurological assessment; depress spontaneous ventilation, prolonged mechanical ventilation duration, increase the incidence of ventilator associated pneumonia (VAP) and lung injury and delirium (1,2,4).

Inadequate sedation will lead to unplanned invasive line removal, self-extubation, interference with effective mechanical ventilation, increased anxiety and may cause long term psychological problems in pediatric age group (3,5,6).

Clinical tools are available to assess the degree of sedation in individual patients; but most of them have limitations in children. No sedation score is gold standard for children admitted in Pediatric Intensive Care Unit (PICU). Several scores are available- Hartwig sedation scale, University of Michigan sedation scale, Neonatal Pain Agitation and Sedation scale, Vancouver Sedative Recovery Scale, Modified Ramsay scale, Penn State Children's hospital sedation algorithm (PENN scale) and Richmond Agitation Sedation Scale (RASS) (6). Comfort scale has been validated to assess sedation in mechanically ventilated children. It consists of 6 behavioural and 3 physiological parameters (HR, BP and RR) (7). As the physiological parameters were found to be influenced by various factors such as use of inotropes, they were omitted. Comfort Behavioural (COMFORT B) score includes only behavioural parameters. Comfort B scale has been validated in critically ill pediatric and neonatal age group (6,8,9).

In adult population, there is good evidence that protocol-directed sedation can reduce the duration of mechanical ventilation, length of ICU stay, length of hospital stay and tracheostomy rates. Sedation in mechanically ventilated adults is now aiming at calm, easily aroused, readily evaluable patient instead of an unresponsive state (10–13). Very little data is currently available on protocol directed sedation in pediatric patients who require mechanical ventilation (14). Most of Pediatric Intensive Care Unit (PICU) mechanically ventilated patients' sedation level is decided by attending paediatrician based on varying parameters. This study will use a protocolized sedation using comfort B scale for determining the optimal sedation level and compare it to non-protocol directed sedation in the control group.

REVIEW OF LITERATURE:

S.no	Journal	Year	Study design and title	Sam-ple	Outcome
1.	Blackwood et al. Journal of American Medical Association(15)	2021	Effect of sedation and ventilator liberation protocol vs usual care on duration of invasive mechanical ventilation in pediatric intensive care - RCT	8843	Significantly shorter time to first successful extubation (64.8hours vs 66.2hours; hazard ratio 1.11, CI 95%; P= 0.02). No significant decrease in the total duration of invasive mechanical ventilation (intervention 2.7 days and control 2.8 days; P = 0.06) and PICU length of stay (intervention – 1.8 days and Control - 2.1 days; P = 0.53)
2.	Saelim et al. Journal pediatric intensive care (16)	2019	Prospective cohort study- Effectiveness of protocolized sedation utilizing comfort B scale in Mechanically ventilated	116	No significant difference in duration of mechanical ventilation (median 4.5 [IQR: 2.2–10.5] vs. 5 [IQR: 3–8.8] days), PICU LOS (median 7 vs. 7 days, P = 0.59) and hospital LOS (median 18 vs. 14 days, P =0.14). Percentages of use of sedative drug use including morphine, fentanyl and midazolam were not statistically different.

			patients in PICU		
3.	Neunhoeffer et al. Pediatric Anaesthesia(17)	2015	Prospective cohort study - Nurse-driven paediatric analgesia and sedation protocol reduces withdrawal symptoms in critically ill medical paediatric patients.	377	There was no significant decrease found in duration of mechanical ventilation (2.02 days (0.96-25) pre vs 1.71 days (0.96 – 66) post implementation. No difference was found in PICU LOS (5.8 days (1-37.75) pre vs 5 days (0.96 – 66) post implementation; P = 0.14), total dose of opioids (3.9 mg/kg/day (0.1-70) pre vs 3.1 mg/kg/day (0.05 – 56) post implementation). But there was a significant decrease in benzodiazepines (5.9 mg/kg/day (0-82) pre vs 4.2 mg/kg/day (0 – 66) post implementation; P = 0.009) post implementation of sedation protocol. Incidence of withdrawal was significantly lower in post implementation period (12.8% vs 23.6%; P = 0.005).
4.	Curley et al. Journal of American	2014	Protocolized sedation vs	2449	Intervention group had no difference in duration of mechanical ventilation

	Medical Association (18)		usual care in paediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial		(intervention: median, 6.5 days [IQR, 4.1-11.2] days; control: median, 6.5 days [IQR, 3.7-12.1] days), inadequate pain and sedation management, iatrogenic withdrawal and unplanned extubation when compared to control. Intervention patients had fewer days of opioid administration (median, 9 days [IQR, 5-15] days; control: median, 10 days [IQR, 4-21] days, P=0.01), were exposed to fewer sedative classes (median, 2 [IQR, 2-3] classes vs 3 [IQR, 2-4] classes; *P* < .001), and were more often awake and calm while intubated(median, 86% [IQR, 67%-100%] of days; 75% [IQR, 50%-100%] of days; P = 0.004) than control patients, respectively; however, intervention patients had more days with any report of a pain score ≥ 4 and any report of agitation.

5.	Jin et al. Journal of Korean Medical Science(19)	2007	Prospective cohort study – The efficacy of the COMFORT scale in assessing optimal sedation in critically ill children requiring mechanical ventilation	42	Compared with the control group, the intervention group showed significant decreases in the total usage of sedatives and analgesics, the duration of mechanical ventilation (11.0 days vs. 12.5 days; P = 0.04) and PICU stay (15.0 days vs. 19.5 days; P = 0.04), and the development of withdrawal symptoms (1 case vs. 7 cases, P = 0.02). The total duration of sedation (8.0 days vs. 11.5 days; P = 0.05) also tended to decrease.

Anxiety, pain and distress lead to agitation which has negative impact on the outcome of the patient. Sedation practices vary widely among institutions and is based on the decision of the treating doctor. In a study conducted by Vet et al., optimal sedation was found in 60% of the population and over sedation was found more frequently than undersedation (31.8% vs 10.6%) (20). Several scales are currently available for the assessment of degree of sedation in critically ill patients to determine the patients' current and desired level of sedation. Most common scale used in North America was found to be State Behavioral Scale (SBS) while in the rest of the countries it was found to be Comfort scale in a survey conducted in 2015 (21). The widely used sedative regimen were found to be a combination of benzodiazepine and opioid in this study (most commonly used opioid was fentanyl and most commonly used

benzodiazepine was found to be midazolam). In order to optimize the sedation given in patients, studies have been done to see the patient outcome when on daily sedation interruption, protocolized sedation and sedation rotation protocols. Randomized Control Trials (RCT) done by Gupta et al. and Veerlat et al. compared the daily interruption of sedation (DSI) and found significant decrease in the duration of mechanical ventilation, percentage dosages of sedatives used and number of days the patient was awake on sedation (22,23). However, another multicenter RCT by Vet et al. found that there was no significant difference in the duration of mechanical ventilation and the amount of sedatives used (20). However, they found significant increase in the 30-day mortality rate but it was considered highly unlikely to be associated with daily sedation interruption (DSI). However, it could not be excluded that the increased mortality was an unexpected impact of the study protocol in that study. Various studies have been done in order to assess the effect of protocolized sedation in mechanically ventilated patients upon various outcomes (24).

A Cochrane review published in 2018 on protocol versus non protocol directed sedation in adults and children included 4 RCTs, of which one was in children. No difference was found in the duration of mechanical ventilation, length of PICU stay and mortality. There was significant reduction in the duration of hospital stay. The authors believed that the benefits of protocol directed sedation remain unclear in mechanically ventilated patients and that further studies are required to comment upon this as the RCTs included in the study had conflicting results (25).

In an unblinded multicenter randomized controlled trial by Blackwood et al., 6^{th} hourly sedation level using the Comfort scale and daily readiness for a spontaneous breathing trial was done by bedside nurse. In this study, a significantly shorter duration to first successful extubation was found in the intervention group when compared to control group (64.8 hours and 66.2 hours $P = 0.02$) but there was no significant decrease in the total duration of

mechanical ventilation or the duration of PICU stay. However, there was a significant decrease in the duration of hospital stay (9.1 days in the intervention group and 9.6 days in the control group; P = 0.01) (15). An unblinded multicenter clustered RCT done in 2015 by Curley et al., where half of the PICUs were randomized into RESTORE (Randomized Evaluation of Sedation Titration for Respiratory Failure) trial, found no statistically significant difference in the duration of mechanical ventilation among the two groups (intervention: median, 6.5 [IQR, 4.1-11.2] days; control: median, 6.5 [IQR, 3.7-12.1] days) (18). In this particular study, 8th hourly assessment of sedation using State Behavioral Scale (SBS), daily extubation readiness trial and pain assessment using Face Legs Activity Cry Consolability (FLACC) scale was done as a part of protocolized sedation. In a prospective cohort study conducted in 2015 by Neunhoeffer et al., in which impact of nurse driven Pediatric Analgesia and Sedation Protocol (pASP) which included 8th hourly sedation assessment was done with the aid of Comfort B scale, Nurse Interpretation of Sedation Score (NISS) and Bispectral Index (BIS). The difference in the duration of mechanical ventilation between the two groups was not statistically significant (17). No significant difference was found in the duration of mechanical ventilation, PICU Length of Stay (LOS) or hospital LOS in a before and after cohort study conducted in 2016 by Saelim et al., in 116 children with a mean age of 22 months. In this study, protocolized sedation using COMFORT B scale assessed every 12h was done by pediatric resident (16). In another cohort study conducted by Dreyfus et al., in which the protocolized study was nurse implemented and included sedation assessment via Comfort B scale 4th hourly, no significant difference was found between the duration of mechanical ventilation in the two groups (26). While in a before and after cohort study conducted by Jin et al., there was statistically significant shorter PICU duration of stay and duration of mechanical ventilation in protocolized sedation in children. In this study, COMFORT B scale was used as sedation tool by the pharmacist to titrate sedation which was being overseen by the attending physician (19).

Significant statistical difference was found between duration of opioid use and dexmedetomidine exposure between the two groups in the RCT by Curley et. al. No difference was found in the amount of opioid use or the other sedative agents used in this study (18). Percentage of sedative drugs (morphine, fentanyl and midazolam) used in the two groups had no statistically significant difference in a cohort study conducted by Saelim et al (16). Also, in Dreyfus' study there was no significant difference in the total amount of sedatives used in both the groups (26). While in the study conducted by Neunhoeffer et al., statistically significant difference was found between mean dosage of opioid use in between the two groups (5.9 mg/kg in control vs 4.9 mg/kg in intervention group) but no difference was found between the use of benzodiazepine use (17). There was a significant reduction in the duration and total amount of sedation in the intervention group in the study by Jin et al (19). In this study, there was also decreased use of neuromuscular blocker (NMB) in the intervention group.

Sedation related adverse events include unplanned extubation, post extubation stridor, extubation failure, unplanned removal of invasive lines, Ventilator associated pneumonia (VAP), greater than or equal to stage 2 immobility related pressure ulcer, reintubation and new tracheostomy (27). In the RCT done by Curley et al., no significant difference was found in sedation related adverse events except with post extubation stridor and stage 2 or worse immobility related pressure ulcer (18). In a study by Dreyfus et al., no difference was found in the unplanned extubation episodes and agitation episodes (26).

Withdrawal assessment tool 1 (WAT 1) has been validated for the assessment of withdrawal syndrome in pediatric patients (28). Withdrawal assessment was done with Sophia Observation Scale (SOS) 8^{th} hourly during weaning in the study by Neunhoeffer et al (17). In this study, incidence of withdrawal syndrome was found to be significantly lower in the post implementation phase. Similar finding was found in the study by Jin et al (19).

Delirium is defined as an acute and potentially reversible impairment of consciousness and cognitive function that fluctuates in severity (29). Incidence of delirium has been reported to be between 8 to 25% in PICUs in studies conducted. It may be decreased with appropriate sedation and analgesia (30,31). In a trial done by Simone et. al., the implementation of a delirium bundle in PICU consisting of protocolized sedation and early mobilization strategy, a significant reduction in the prevalence of delirium was found (32).

PIM 3 (Pediatric Index of Mortality 3) score has been validated as a reliable predictor of mortality in children admitted in PICU (33,34). This score can be used to calculate the probability of mortality as a percentage.

Analgesia is defined as the control of pain in the form of diminution or elimination of pain (35). Self reporting of pain is considered the gold standard for pain assessment. FLACC scale has been validated for pain assessment in mechanically ventilated patients between 0-7 years of age (36). Numerical rating scale has been validated in children aged 8 to 18 years for pain assessment (37). There was increased days with episode of pain and aggression in the intervention group in the RCT by Curley et al., but the days to first wakeful calm state was less.

Lacunae in existing knowledge:

There is not much evidence regarding protocolized sedation in pediatric age group to conclude regarding effectiveness or ineffectiveness in determining LOS and sedative drug usage. Only 2 RCTs were found till date which used Comfort scale and State Behavioural Scale respectively for protocolized sedation and were found to have conflicting impact on outcome of the mechanically ventilated children admitted in PICU (15,18).

RESEARCH QUESTION:

Does protocol directed sedation using comfort B scale in mechanically ventilated children aged 1 month to 18 years of age decrease the duration of mechanical ventilation over non protocol directed sedation?

AIMS AND OBJECTIVES:

AIM: To compare the effectiveness of protocolized sedation in mechanically ventilated patients aged 1month to 18 years when compared to non-protocol directed sedation.

Primary Objectives:

- To determine the effect of protocolized sedation using comfort B scale on the duration of mechanical ventilation.

Secondary objectives:

- To compare the amount of usage of various sedative drugs in protocolized sedation with usual care.
- To compare the frequency of accidental extubation, reintubations, removal of an invasive line between the 2 groups
- To compare the incidence of VAP and ≥ stage 2 pressure ulcers between the two groups
- To compare the incidence of tracheostomy between the 2 groups.
- To compare the incidence of withdrawal symptoms using withdrawal assessment tool- version 1 (WAT 1) in patients on benzodiazepine (BZD) and opioid use for more than 5 days.
- To compare pain score between the 2 groups using FLACC (face, legs, activity, cry, consolability) scale for children aged equal to or less than 7 years and numeric rating scale for age > 7 years.
- To compare the PICU length of stay and hospital length of stay between the 2 groups.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES:

Study design: Randomized control trial with 1:1 ratio. Randomization was done by computer generated variable block randomization. Randomization was maintained via opaque sealed envelopes.

Study setting: Pediatric Intensive Care Unit, AIIMS Jodhpur.

Ethical Approval: Ethical approval was obtained from institutional ethical committee, AIIMS Jodhpur (AIIMS/IEC/2019-20/980).

Trial Registry: The trial was registered with Clinical Trials Registry India (CTRI) - (Registration number: CTRI/2021/04/033130).

Eligibility criteria:

- **Inclusion criteria:**

1. Children between one month to 18 years whose anticipated length of mechanical ventilation was more than 24 hours.
2. Parents or guardians who gave informed written consent for enrollment of their child into the study

- **Exclusion criteria:**

1. Patients with neurological disease as the COMFORT B scale cannot be used to determine the level of sedation.
2. Patients who required deeper sedation for treatment as in pulmonary HTN or severe ARDS requiring high frequency oscillatory ventilation.

Data collection:

1. COMFORT B scale was introduced to residents posted in PICU 4 weeks prior to period of data collection for better implementation. Residents were trained to use the sedation scale during this period.

2. Informed written consent was obtained from parents/legally authorized representative. The purpose and design of study was explained to the child's parents.

3. Initial collection of baseline data, diagnosis and PIM3 score was done. Randomization was done into intervention and control groups.

4. Implementation of protocolized sedation in the intervention group.

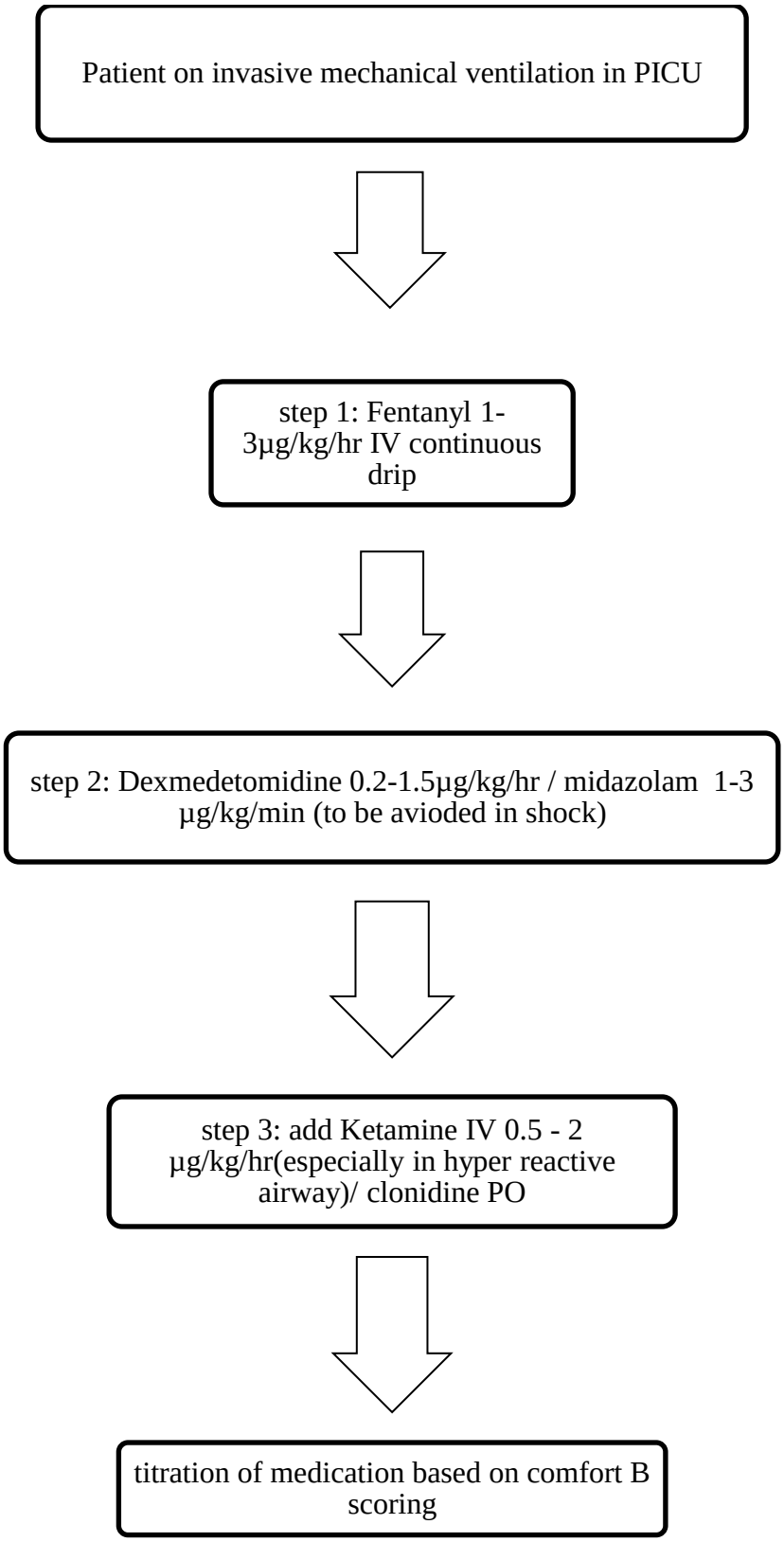
5. 4^{th} hourly COMFORT B scoring and titration of sedation in response to it.

6. Daily assessment of pain using FLACC scale (age $\leq$ 7 years age) and numerical rating scale (age > 7 years) as applicable.

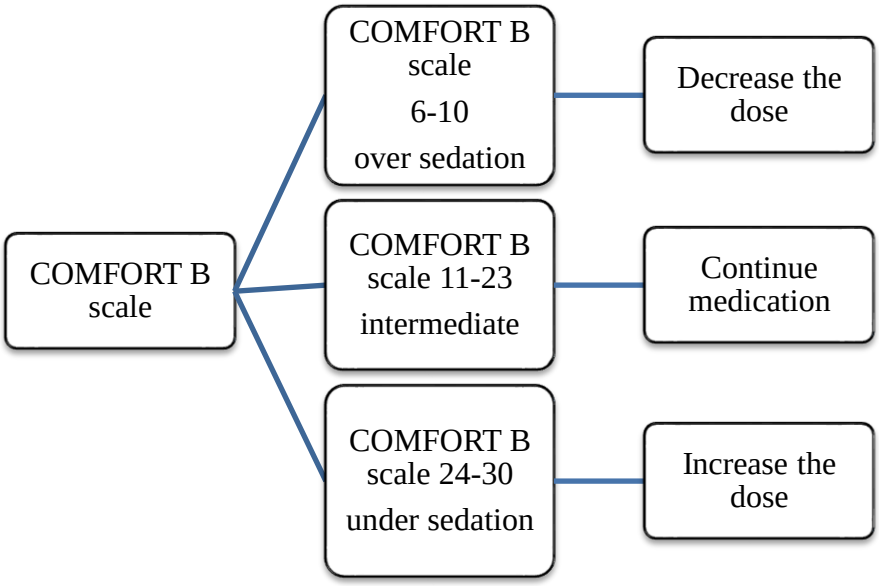
7. Weaning from sedation as per guidelines and assessment of withdrawal using WAT 1 score.

8. Collection of patient data regarding duration of MV, PICU LOS, hospital LOS, PICU discharge status, number of reintubations, self extubation, accidental removal of invasive lines, incidence of VAP, central line associated blood stream infections (CLABSI), delirium, incidence of $\geq$ stage 2 pressure ulcers, incidence of tracheostomy, post extubation stridor, time required for weaning and sedatives used.

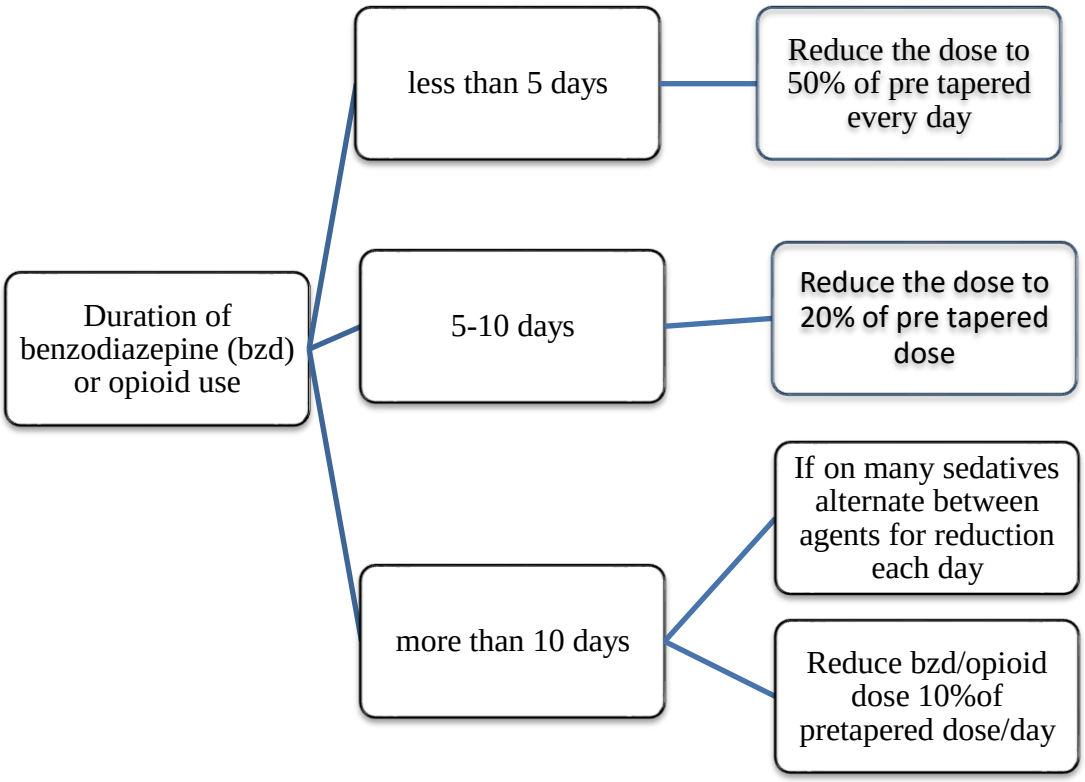
Sedation Protocol:



Titration of sedation based on Comfort B score:



Opioids and benzodiazepines tapering guidelines



a. Initiate withdrawal assessment tool every 4h and continue for 1-2 days after all opioids and benzodiazepines have been stopped (38).

b. If withdrawal symptoms or scores do not improve or worsen:

I. Increase last agent weaned to previous dose.

II. Add or increase clonidine.

Assessment of sedation:

The Comfort-B scale used in this study is a behavioural clinical scale that consists of six factors: alertness, calmness/agitation, respiratory response (or crying, used in patients with no MV), physical movement, muscle tone, and facial tension. Each factor can be scored with values ranging between 1 and 5, generating scores between 6 and 30 points. Scores between 6 and 10 indicate over sedation; scores between 11 and 23 indicate a moderately sedated patient; and scores between 24 and 30 indicate little sedation (6).

Sample size:

The calculated sample size for our study when calculated with a power of 80% with alpha error 0.05 (standard deviation in group 1 was taken as 17.7 and in group 2 was 13) came to be 237 in each group which was not possible to achieve in the given duration in our 8 bedded PICU. Therefore, all the children meeting the eligibility criteria admitted in our PICU during the period from March 2020 to August 2021 were enrolled in this study.

Statistical methods:

Statistical analyses were performed by SPSS version 27.0 (released 2020, Armonk, NY: IBM Corp). Categorical and continuous values were expressed as frequency (percentage) and mean ± SD or median and interquartile range (IQR) as appropriate. Descriptive statistics were used to summarise demographic data, medical diagnosis, and clinical characteristics of the patients. Associations between two or more qualitative variables were assessed using chi-square test and Fisher Exact test as appropriate. Quantitative data between the two independent groups were analysed using unpaired 't' and Mann Whitney U tests as appropriate.

ETHICAL JUSTIFICATION

1. This study was undertaken only after obtaining ethical clearance and receiving the approval from the Institute's Ethics committee.

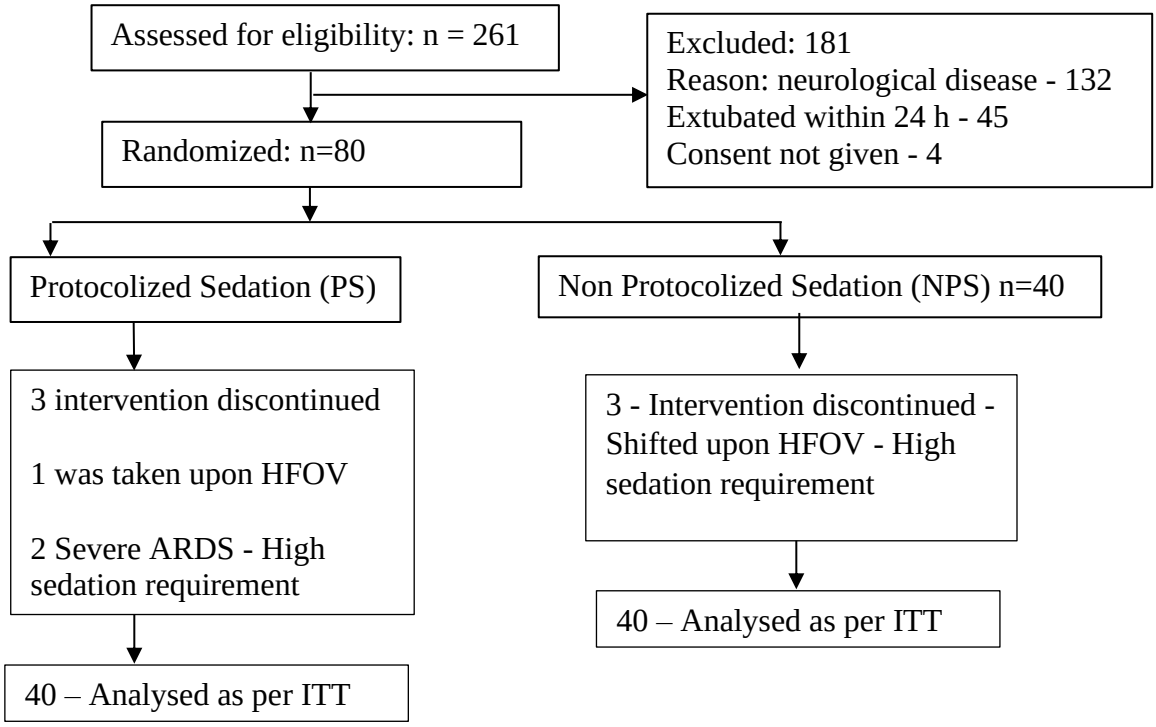
2. Children were enrolled after obtaining informed consent from parents/ guardians.

3. The participation in the study in no way changed or compromised the management of these children.

RESULTS

A total of 261 patients were assessed for eligibility for this study who were admitted in PICU during the study period. 181 were excluded of which 132 had neurological disease, 45 were extubated within 24 hours and 4 did not give consent. 80 were included in this study who were randomized into 2 groups - protocolized sedation (PS) and non-protocolized sedation (NPS). In PS group, intervention was discontinued in 3 patients as the patients required high sedation (one was shifted upon high frequency oscillation ventilation (HFOV) and 2 developed severe acute respiratory distress syndrome (ARDS). In NPS group, 3 were shifted upon HFOV, requiring higher sedation and neuromuscular blockade. All the patients were included in the analysis as per intention to treat analysis.

Figure 1: CONSORT flow diagram of the study



NPS- Non Protocolized sedation; PS - Protocolized sedation; HFOv- High frequency Oscillation ventilation; ARDS- acute respiratory distress syndrome; ITT- Intention to treat.

Demographic data:

Median age of the population in PS group was 4.5 years (IQR 0.93, 12.75) and in NPS group 1.5 years (IQR 0.6,6) with no significant difference (P = 0.07).

In our study, 62.5% of the intervention group (n= 25) and 67.5% of the control group (n= 27) were found to be males. No statistically significant difference was found between them (P = 0.64).

Most common diagnostic category in both the groups was found to be respiratory (42%: n = 17 in PS group and 45%: n = 18 in NPS group) followed by postoperative patients (32.5%: n = 13 in NPS and 27.5%: n = 11 in PS group). It was found that there were 5 cardiac (12.5%), 3 hemato-oncology (7.5%) and 2 patients in endocrine (5%), 1 each in renal and GIT categories (2.5%) in the PS group. There were 5 cardiac cases (12.5%), 1 GIT cases (2.5%), 1 renal patient (2.5%, 1 hemato-oncology (2.5%) and nil endocrine cases in the NPS group. No statistically significant difference was found in the number of patients in each diagnostic category between the two groups (P= 0.63).

Median PIM3 score of the PS group which was calculated at admission was -2.13 (IQR 0.76, 24.3) and that of NPS group was -3.92 (-5.83, -1.49) which also had no significant difference (P = 0.12). In the PS group, the calculated median probability of mortality from PIM3 score at admission was 11.78 (0.76,24.3) while in NPS group it was 2.15 (0.03,18.32) with no significant difference (P = 0.12). The mortality of study population in intervention group was 35% (n = 14) in PS group and 32.5% (n = 13) in NPS group with no statistically significant difference (P = 0.69).

Table 1: Demographic Data

	Protocolized Sedation (n = 40)	**Non protocolized Sedation (n = 40)**	**P Value (two sided)**
Age (Years), Median (IQR)	4.5 (0.93,12.75)	1.5 (0.6,6)	0.07
Male, n (%)	25 (62.5%)	27 (67.5%)	0.64
Diagnosis			0.63
Respiratory, n (%)	17 (42%)	18 (45%)	
cardiac, n (%)	5 (12.5%)	5 (12.5%)	
Endocrine, n (%)	2 (5%)	0 (0%)	
Renal, n (%)	1 (2.5%)	1 (2.5%)	
GIT, n (%)	1 (2.5%)	1 (2.5%)	
Hemato-oncology, n (%)	3 (7.5%)	1 (2.5%)	
Postoperative, n (%)	11 (27.5%)	13 (32.5%)	
PIM3 scale n, median (IQR)	-2.13 (-4.93, –1.13)	-3.92 (-5.83, -1.49)	0.12
Probability of mortality, median (IQR)	11.78 (0.76,24.3)	2.15 (0.03,18.32)	0.12
Mortality, n (%)	14 (35%)	13 (32.5%)	0.69

GIT- Gastrointestinal tract, PIM3- Pediatric Index of Mortality 3, IQR – Interquartile Range

Comparison of outcomes between the two groups

The median duration of mechanical ventilation (MV) of PS group was found to be 3.5 days (IQR 3, 7) and that of NPS group was 8.5 days (IQR 4.25, 13.75) with significant difference (P = 0.008). The PICU length of stay was found to be significantly shorter in the PS group in comparison with NPS group (6.5 days: IQR 3,11.5 in PS group and 10 days: IQR 6.25, 22.5 in the control group; P=0.002).

The median hospital length of stay was found to be 13 days (IQR 6.25, 21.75) in PS group and 26.5 days (IQR 10, 31.5) in NPS group but was found to be statistically insignificant (P = 0.07).

Patients were found to be awake and calm for a mean duration of 2.03 days (3.26 SD) in PS group and 3.63 days (6.4 SD) in NPS group (statistically insignificant; P=0.89). Mean duration to first awake and calm state following intubation and sedation in PS group was found to be 3 days (4.49 SD) and 6 days (8.58 SD) in NPS group with no statistically significant difference (P = 0.23).

In PS group, the median days with pain score less than 4 was found to be 3 days (IQR 2, 7.75). While in NPS group, it was found to be 8 days (IQR 3, 16.5) (P = 0.02). The mean days during the study period with pain score more than 4 was found to be 0.48 days (1.45 SD) in PS group and 1.9 days (3.84 SD) in NPS groups (P = 0.007). Both days with pain score less than 4 and more than or equal to 4 were found to be decreased in the PS group in comparison to NPS group.

5% (n = 2) of the PS group were tracheostomized while 10% (n = 4) of the NPS group were found to be tracheostomized during the study period with no

significant difference (P = 0.68). Post extubation stridor was present in 2.5% (n = 1) in PS group in comparison to 20% (n = 8) in NPS group (P = 0.02).

There was usage of intermittent bolus dose of neuromuscular blocker for a mean duration of 0.2 days (1.11 SD) in PS group and 0.48 days in the patients in NPS group without any statistically significant difference (P = 0.142). 80% (n = 32) of the PS group needed inotropic support in comparison to 47.5% (n = 19) of the NPS group (P = 0.002).

Table 2: Comparison of Outcomes between the two groups

	Protocolized Sedation (n=40)	**Non Protocolized Sedation (n=40)**	**P Value (two sided)**
MV duration (days), median (IQR)	3.5 (3, 7)	8.5 (4.25, 13.75)	0.008
PICU LOS (days), median (IQR)	6.5 (3, 11.25)	10 (6.25, 22.5)	0.002
Hospital LOS (days), median (IQR)	13 (6.25, 21.75)	16.5 (10, 31.5)	0.054
Study days awake and calm (days), mean (SD)	2.03 (3.26)	3.63 (6.4)	0.89
Days to first calm state (Days), mean (SD)	3 (4.49)	6 (8.58)	0.23

Study days with pain score <4 (Days), median (IQR)	3 (2.7.75)	8 (3,16.5)	0.02
Study days with pain score ≥ 4 (Days), mean (SD)	0.48 (1.45)	1.9 (3.84)	0.007
Incidence of tracheostomy, n (%)	2 (5%)	4 (10%)	0.68
Post extubation stridor, n (%)	1 (2.5%)	8 (20%)	0.02
Inotropic support, n (%)	32 (80%)	19 (47.5%)	0.002
Days requiring NMB usage (Days), mean (SD)	0.2 (1.11)	0.48 (1.48)	0.142

MV- Mechanical Ventilation, PICU- Pediatric Intensive Care Unit, LOS – Length of Stay, IQR – Interquartile Range, NMB – Neuromuscular Blocker; SD – standard deviation

Sedation related adverse events

Ventilator associated Pneumonia (VAP) was found in 5% of PS group (n=2) while it was found in 42.5% of NPS group (n = 17) during the study period (P = <0.001).

The incidence of Central line associated blood stream infection (CLABSI) in the intervention group was found to be 5% (n = 2) and in the control group was 7.5% (n = 3) without any statistically significant difference (P=0.64).

No significant difference was found in mean episodes of reintubation between the two groups (P=0.11). Mean episodes of reintubation was 0.3 (0.69 SD) in PS group and 0.65 (1.05 SD) in NPS group. Mean incidence of extubation failure in PS group was 0.15 (0.43 SD) while it was 0.38 (0.81 SD) in NPS group with no statistically significant difference (P=0.21). There was statistically significant increased mean incidence of self extubation in NPS group (mean = 0.25 ± 0.49 SD) in comparison to PS group (mean 0.025 ± 0.16 SD; P = 0.007).

Mean incidence of accidental removal of invasive lines was found to be nil in PS group and 0.1 (0.38 SD) in NPS group (P=0.08).

No statistically significant difference was found in the incidence of clinically significant (≥ stage 2) pressure ulcer which was found to be 7.5% (n = 3) in NPS group and 2.5% (n = 1) in PS group (P=0.62).

There was no significant difference in the incidence of delirium (P = 0.24) which was found to be 7.5% (n = 3) in NPS group and nil in PS group.

Incidence of withdrawal syndrome (WAT 1 score ≥ 3) was found to be 5% (n = 2) in PS group and 20% (n = 8) in NPS group (P = 0.08). The mean duration with WAT 1 score ≥ 3 was found to be significantly more in the NPS group (mean 11.04 ± 19.44 hrs) when compared to PS group (mean 0.96 ± 4.8 SD) (P

= 0.02). Mean peak WAT 1 score was found to be higher in NPS group which was 1.23 (1.42 SD) in comparison to PS group which was 0.16 (0.62 SD) (P <0.001).

The mean duration required for weaning was found to be 2.02 days (1.71 SD) in PS group and 2.88 days (3.18 SD) in NPS group with no statistically significant difference (P = 0.93).

Table 3: Comparison of Sedation related adverse Events between the two groups

	PS (n=40)	**NPS (n=40)**	**P value (two sided)**
Incidence of VAP, n (%)	2 (5%)	17 (42.5%)	<0.001
Incidence of CLABSI, n (%)	2 (5%)	3 (7.5%)	0.64
Episodes of reintubation, mean (SD)	0.3 (0.69)	0.65 (1.05)	0.11
Incidence of extubation failure, mean (SD)	0.15 (0.43)	0.38 (0.81)	0.21
Incidence of self extubation, mean (SD)	0.025 (0.16)	0.25 (0.49)	0.007
Episodes of accidental removal	0(0)	0.1 (0.38)	0.08

of invasive lines, mean (SD)			
Incidence of immobility related pressure ulcer (stage≥2), n (%)	1(2.5%)	3 (7.5%)	0.62
Incidence of delirium, n (%)	0 (0)	3 (7.5%)	0.24
Withdrawal syndrome (WAT 1 score ≥ 3), n (%)	2 (5%)	8 (20%)	0.08
Duration with WAT 1 score ≥ 3 (hours), mean (SD)	0.96 (4.8)	11.04 (19.44)	0.02
Peak WAT 1 score, mean (SD)	0.16 (0.62)	1.23 (1.42)	<0.001
Time required for weaning (Days), mean (SD)	2.02 (1.71)	2.88 (3.18)	0.93

NPS – Non Protocolized sedation, PS – Protocolized Sedation, VAP – Ventilator Associated Pneumonia, CLABSI – Central Line Associated Blood Stream Infection, WAT 3 – Withdrawal Assessment Tool 3, SD – Standard Deviation

Doses and days of exposure to sedative agents

There was no significant difference in median dose of fentanyl used in PS group (1.25 μ/kg/hr IQR 0.86, 1.85) in comparison to NPS group (1.46 μ/kg/hr IQR 1, 2.21; P = 0.09). The cumulative dose and duration of exposure of fentanyl in PS group was significantly lower than NPS group (P = 0.007 and P = 0.009 respectively). The cumulative dose of fentanyl used in PS group was found to be 120μ/kg (IQR – 62.88, 279.12) and that of NPS group was 320.4μg/kg (IQR 110.88, 851.52). The median duration of exposure to fentanyl was 4 days (IQR 2.25, 7.75) in PS group and 8 days (IQR 4, 17.5) in NPS group.

The median dose of dexmedetomidine used was found to be 0.23μg/kg/hr (IQR 0, 0.43) in PS group and 0.34μg/kg/hr (IQR 0, 0.68) in NPS group with no statistically significant difference (P = 0.27). The cumulative dose of dexmedetomidine used was found to be 44.8 μg/kg ± 143.52 in PS group and 121.2 μg/kg ± 278.16 in NPS group with no significant difference (P = 0.195). Median duration of exposure to dexmedetomidine was found to be 2.18 days (IQR – 0, 2.75) in PS group and 4.9 days (IQR – 0, 7.25) in NPS group without any significant difference (P = 0.197).

The median dose of midazolam used in PS group was found to be 0.93 mcg/kg/min (IQR – 0, 1.29) which was found to be significantly less when compared to that in NPS group (median dose 1.1; IQR - 0.87, 2.22; P = 0.003). The cumulative dose of midazolam used in PS group was found to be 4.32mg/kg (IQR 0, 9.17) which was significantly less when compared to that of NPS group which was 8.93 mg/kg (IQR 1.44, 36) (P = 0.005). There was no difference in the median duration of exposure to midazolam in PS group (3 days IQR - 0, 5.75) when compared to NPS group (4 days IQR - 1, 11; P = 0.096).

In our study, we found a significantly decreased mean dose of ketamine used in PS group (mean dose 0.07 mg/kg/hr ± 0.24) in comparison to that of NPS group (Mean dose 0.59 mg/kg/hr ± 0.91; P = 0.003). The cumulative dose of ketamine

used was found to be 10.08 mg/kg ± 42 which was significantly less when compared to NPS group (cumulative dose 108.96 mg/kg ± 282; P = 0.005). The mean duration of exposure to ketamine was found to be 0.5 days ± 1.92 in PS group which was significantly less than that of NPS group (2.52 days ± 6.24; P = 0.007).

The mean dose of clonidine used in NPS group was 0.49 μg/day ± 2.29 SD and 0 in PS group with no significant difference (P = 0.16). The cumulative dose of clonidine used in NPS group was 1.78 μg ± 8.39 and 0 in PS group (P = 0.16). The mean duration of exposure to clonidine was 0.18 days ± 0.82 in NPS group in comparison to PS group (0 days) with no significant difference (P = 0.16).

The median number of sedative classes used in PS group was 2.15 (IQR 1, 3) which was significantly less than NPS group (2.58 classes IQR 2, 3; P = 0.03).

Table 4: Effect of protocolized sedation on doses and days of exposure to sedative agents

	PS (n=40)	NPS (n=40)	P value (2 sided)
Fentanyl avg dose (μg/kg/hr), median (IQR)	1.25 (0.86,1.85)	1.46 (1,2.21)	0.09
Fentanyl cumulative dose (μg/kg), median (IQR)	120 (62.88,279.12)	320.4 (110.88,851.52)	0.007
Days of exposure to Fentanyl (days), median (IQR)	4 (2.25,7.75)	8 (4,17.5)	0.009

Dexmedetomidine avg dose (µg/kg/hr), median (IQR)	0.23 (0,0.43)	0.34 (0,0.68)	0.27
Dexmedetomidine cumulative dose (µg/kg), mean (SD)	44.88 (143.52)	121.2 (278.16)	0.195
Days of exposure to dexmedetomidine (days), median (IQR)	2.18 (0,2.75)	4.9 (0,7.25)	0.197
Midazolam avg dose (mcg/kg/min), median (IQR)	0.93 (0,1.29)	1.1 (0.87,2.22)	0.003
Midazolam cumulative dose (mg/kg), median (IQR)	4.32 (0,9.17)	8.93 (1.44,36)	0.005
Days of exposure to midazolam (days), median (IQR)	3 (0,5.75)	4 (1,11)	0.096
Ketamine avg dose (mg/kg/hr), mean (SD)	0.07 (0.24)	0.59(0.91)	0.003
Ketamine cumulative dose	10.08 (42)	108.96 (282)	0.005

(mg/kg), mean (SD)			
Days of exposure to ketamine (days), mean (SD)	0.5 (1.92)	2.52 (6.24)	0.007
Clonidine avg dose (µg/day), mean (SD)	0 (0)	0.49 (2.29)	0.16
Clonidine cumulative dose (µg), mean (SD)	0 (0)	1.78 (8.39)	0.16
Days of exposure to clonidine (days), mean (SD)	0 (0)	0.18 (0.82)	0.16
Sedative classes, median (IQR)	2.15 (1,3)	2.58 (2,3)	0.03

PS Protocolized Sedation NPS Non Protocolized Sedation. IQR Interquartile Range, SD – standard deviation, avg – average.

DISCUSSION

Critically ill patients admitted in PICU require some form of sedation which can be achieved using various sedative agents such as benzodiazepines and opioids. Objective assessment of optimum sedation level is a must to decrease the use of sedative agents, sedation related adverse events, morbidity and duration of mechanical ventilation and duration of PICU stay which may be achieved using protocolized sedation with the aid of various sedative scales. There is a paucity of literature on the use of protocolized sedation in children in comparison to adults, more so from our country. Previously, cohort studies have been done with implementation of COMFORT B scale for protocolized sedation in numerous ways with conflicting results. Our study is a RCT which aims to add robust evidence to the existing literature regarding the outcome of protocolized sedation in PICU.

In our study, the median age of study population was found to be 2 years (IQR 0.8, 10.75). In comparison, the median age of the study population was found to be 22.3 months (IQR 6.6, 68.4) in a study by Saelim et al (16). We found a median age of 4.5 years (IQR - 0.93, 12.75) and 1.5 years (IQR 0.6,6) in PS and NPS group in our study respectively. In the study by Dreyfus et al., the median age in PS and NPS group were found to be 2.2 (IQR 0.4, 9.6) and 3.2 years (0.4, 9.7) respectively (26). While it was found to be 3.31 years (IQR 0, 18) and 2.95 years (IQR 0, 18) in PS and NPS group respectively in a study by Neunhoeffer et al (17). In another study by Curley et. al., median age was found to be 1.4 (IQR 0.3, 7) and 2.6 years (IQR 0.6, 9.2) in the intervention and control group respectively (18). Our study had a relatively older population when compared to previous studies.

62.5% (n = 25) males and 67.5% (n = 27) males were found in PS and NPS group in our study respectively. 46.6% (n = 27) and 55.2% (n = 32) males were found in PS group and NPS group respectively in the study by Saelim et al. (16) While 54% (n = 667) and 56% (n = 681) males were found in PS and NPS group

in the study by Curley et al (18). In the study by Neunhoeffer et al., the PS group had 47% (n =87) males and NPS group had 53% (n = 81) male population respectively (17). 59% (n = 61) and 61% (n = 57) males were respectively found in PS and NPS group in the study by Dreyfus et al (26). While 38% (n = 8) and 45% (n = 9) males were found in the PS and NPS group by Jin et al (19). Compared to previous study, our study population comprised predominantly of male children. This may be because in our part of the country, boys are given more priority when compared to girls when it comes to providing medical care by the parents.

Our study included heterogenous group of population with various diagnosis unlike the study by Hanser et al., who included homogenous population (Postoperative Tetralogy of Fallot patients) (39). In our study, the most common diagnostic category was found to be respiratory followed by postoperative and cardiac in both the intervention and control group. Cardiac (47%; n = 55), postoperative patient group (n = 64; 55.1%) and hemato-oncology (17%, n = 14.6) were found to be the common diagnostic group in the study by Saelim et al (16). The study by Curley et al., found the most common diagnosis to be pneumonia, bronchiolitis followed by acute respiratory failure secondary to sepsis (18). Dreyfus' et al. found most of their PICU admissions to be neurological followed by post-surgical, respiratory followed by sepsis (26). Study by Gaillard le Roux et al., found the predominant diagnostic category in their study population to be postoperative followed by respiratory, sepsis and neurological cases (40).

In our study, no significant difference was found in the severity of disease measured by the aid of PIM3 score predicting the mortality at admission between the two groups. This was in line with the finding by Neunhoeffer et. al., Gaillard – Le Roux et. al., and Dreyfus et. al., who found no difference in PMODS, PIM2 and PELOD score, respectively used as a marker of severity of disease, in the PS and NPS groups (17,26,40). Also, no difference was found in severity of disease between the two groups, in the studies by Neunhoeffer et al.

and Jin et al. who used PMODS and PRISM 3 score respectively (17,19). PRISM 3 score, used in the study by Saelim et al., was found to be significantly higher in the PS group (16). Also, when used in the RCT by Curley et al. PRISM 3 score was found to be significantly higher in the control group (18).

The mortality rate between the intervention and control group in our study had no significant statistical difference in line with the findings in studies by Dreyfus et al., Curley et al., and Saelim et al (16,18,26).

In our study, the duration of mechanical ventilation and PICU length of stay were found to be significantly less in PS group when compared to NPS group. However, we found no significant difference in the hospital length of stay between the two groups. This was in line with the finding by Jin et al who found a significant decrease in the duration of MV and length of PICU stay (19). Also, in a RCT by Blackwood et al., in which sedation and ventilation liberation protocol using COMFORT scale was used, a significant reduction was found between the hospital LOS and duration of invasive mechanical ventilation in PS group in comparison to NPS group, but no significant difference was found in PICU LOS (15). In the study by Hanser et al., there was a significant decrease in PICU LOS but no difference was found in duration of MV in a homogenous population (Post-operative TOF patients) (39). In contrast to our finding, no significant difference was found in the duration of MV, PICU LOS or hospital LOS between the two groups in studies by Neunhoeffer et al., Saelim et al., Dreyfus et al., Gaillard Le Roux et al. and Curley et al (16–18,26,40). This may be attributed to the fact that the median age of our study population was higher when compared to the previous studies. As was found in the study by Gaillard et al., there was no difference in the duration of MV between the two groups but when they did subgroup analysis, they found that there was a significant reduction in the duration of MV in children more than 1 year of age (40). It may be because of reluctance to decrease the sedation in younger children in fear of accidental extubation and difficulty in assessing scores in younger children (18). Also the sedation scoring in our study was done by pediatric residents

while in the other studies sedation scoring was mostly nurse driven. It was speculated in a study by Ista et al., that nurses prioritized patient comfort to decreasing length of stay thereby targeting higher sedation scores which may have resulted in difference in our findings with that of the other studies (41).

In our study, no significant decrease was found in the days to first awake and calm state and median duration of awake and calm days in the PS group. In contrast, Curley et al., found that the awake and calm days were significantly higher in PS group. However, even they found no difference in the days to first calm state. This difference may be due to the difference in sedation scale used (Comfort B scale in our study and SBS in their study) (18).

In our study, we found that both the study days with pain score <4 and days with pain score ≥ 4 were found to be significantly higher in NPS group in comparison to PS group which may be due to significantly higher total duration of MV and sedation in the NPS group. The RCT by Curley et al., using SBS scale found that there were significantly higher study days with pain score ≥ 4 and episode of agitation in PS group. But they found that no difference in days with pain score < 4 (18). This may be because they had a statistically significant younger population in PS group and significantly more patients with bronchiolitis as primary diagnosis in PS group when compared to NPS group. This may have resulted in more challenging sedation and pain control in view of difficulty in assessing and more active study population.

In our study, there was no difference in the incidence of tracheostomy between PS and NPS groups in line with the findings by Curley et al. and Blackwood et al (15,18).

In our study, a significantly higher incidence of post extubation stridor was found in NPS group. In contrast, no significant difference was found in study by Blackwood et al. but increased stridor was seen in PS group by Curley et al (15,18). The reason for increased stridor in PS group found by Curley et. al.

may be the result of increased days with pain score more than 4 and agitation episodes in PS group in their study.

Patients requiring inotropic support was significantly higher in PS group in our study. However, no difference was found by Saelim et al. and Dreyfus et al (16,26). The choice of sedation used in the protocol and diagnosis of the population group in our study was different when compared to theirs which may have resulted in this conflicting findings. On the other hand, it was found to be significantly higher in NPS group in study by Gaillard Le Roux et al (40). It may be due to significantly increased doses of midazolam used in NPS group in the study by Gaillard et al (40).

No significant difference was found in days requiring usage of NMB in our study. Similar finding was seen in the studies by Curley et al., Dreyfus et al. and Gaillard et al (18,26,40). Jin et al. however, found a significant decrease in the usage of NMB following introduction of PS (19). Their study was a cohort study with comparison group being historical control. This difference in findings could have been because of changing treatment policy and improving quality of medical care with time.

We found decreased incidence of VAP in PS group while no difference was found in the study by Curley et al. (18) and Gaillard et al (40). As a result of increased duration of MV secondary to sedation and requirement of frequent suctioning, there may be increased risk of VAP especially in a developing country like ours with a high infection rate.

We found incidence of CLABSI to be the same within the two groups in line with the finding by Curley et al (18). Though higher rates have been reported in an adult study in NPS group probably because of increased requirement of continuous sedation infusion (25).

In our study, we found a decreased mean rate of accidental self extubation in PS group but no difference in the rate of reintubation or extubation failure.

Gaillard et al. and Hanser et al. found no difference in extubation failure and Blackwood et al. found no difference in the reintubation rate between the 2 groups (15,29,40). Curley et al., Saelim et al., Neunhoeffer et al. and Dreyfus et al., found no difference in the rate of accidental self extubation (17,18,26). Adequate sedation and analgesia may be the cause of lower accidental extubation rate in PS group in our study. Other factors such as underlying disease could have more influence on rate of extubation failure and reintubation which led to no difference.

In our study, no significant association was found between immobility related ≥ stage 2 pressure ulcer and PS. But Curley et al. found a significant reduction in the incidence of immobility related pressure ulcers in PS group (18). Likely the difference may be because of the difference of sedation scores used and goals of sedation in the two studies (18). Also, in our study we found no significant difference in the incidence of delirium when PS was used. Though in previous studies, it has been found that decreased exposure to benzodiazepine and optimum sedation results in decreased incidence of delirium (42).

In our study, we found a significant decrease in the duration with WAT 1 score ≥ 3 and peak WAT 1 score in PS group but no difference was found in the incidence of withdrawal syndrome (WAT 1 score ≥ 3) between the two groups. But Neunhoeffer et al. found a significant decrease in the incidence of withdrawal syndrome assessed by Sophia Observation scale (SOS) post implementation of sedation protocol in 2015 and 2017 (17,43). Modified Finnigan score was used by Jin et al. and they found a significant decrease in incidence and severity of withdrawal (19). Also, Dreyfus et al. found that there was decreased incidence of withdrawal symptoms post PS implementation using WAT 1 score (26). Contrarily, there was no difference in occurrence of withdrawal symptoms in the study by Gaillard et al. and iatrogenic withdrawal syndrome by Curley et al. assessed by the aid of WAT 1 score (18,40). The varying results may be due to the difference in the tools used for assessment of withdrawal syndrome and sedative agents used in the

protocolized sedation. The decrease in peak WAT 1 score and duration with withdrawal in PS group in our study may be because of the decreased use of sedative agents in the PS group in comparison to NPS group.

In our study, no difference was found in the time required for weaning off sedation in line with finding by Curley et al (18).

In our study, we found significantly reduced cumulative dose and duration of exposure to fentanyl. Also, we found decreased average and cumulative dose of midazolam in PS in comparison to NPS group. However, no difference was found in the average dose of fentanyl and days of exposure to midazolam. Curley et al. also found significant decrease in total duration of exposure to opioids and number of opioids and benzodiazepines used. However, they found no difference in the mean dose, peak dose and cumulative dose of benzodiazepine and opioid used in both the study groups (18). Hanser et al. and Jin et al. found a significant decrease in the use of opioid and benzodiazepine in PS group (19,39). Gaillard et al. found a significant difference in the daily dose of benzodiazepine but found no difference in the duration or daily dose of opioid (40). Neunhoeffer et al. found a significant decrease in the total dose of benzodiazepine but no difference was found in that of opioid (17,43). In contrast, Dreyfus et al. and Saelim et al. found no difference in the average dose of opioid and benzodiazepine used in both the groups (16,26). Overall a decreased dose and duration of exposure to benzodiazepines and opioids was found in our study and as well as in many other studies with the use of protocolized sedation. This may lead to decrease in the adverse events of sedative agents and their deleterious effect on cognition in young children on long term follow up.

We found significantly reduced mean dose, cumulative dose and duration of exposure to ketamine in PS group in our study. Gaillard et al. and Jin et al. also found a decrease in length of exposure and usage of ketamine respectively while Curley et al. found no difference (18,19,40). However in our study, no

difference was found in the mean dose or cumulative dose or duration of exposure to dexmedetomidine and clonidine between the two groups in line with the finding by Curley et al. and Dreyfus et al. but Hanser et al. found an increase in use of clonidine following implementation of PS (18,26,39). This may be attributed to difference in the sedative agents used in protocol of the various studies. Overall, in our study, there was significant reduction in sedative classes used in PS group when compared to NPS group in line with the findings of Curley et al (18). Decreased number, dose and duration of exposure to sedative drugs that is found with the use of protocolized sedation will lead to decrease in the incidence of immediate and late onset sedation related adverse events and morbidity.

Limitations:

1. Convenient sampling.
2. Study was done with multiple assessors.
3. Single centre study.

Strength of the study

1. Randomized controlled trial
2. First RCT in India comparing protocolized sedation with non-protocolized sedation in mechanically ventilated children.
3. First RCT to use COMFORT B scale for protocolized sedation to the best of our knowledge.

Conclusion

We found a decrease in MV duration, PICU LOS, sedation related adverse events such as incidence of VAP, incidence of accidental self extubation, post extubation stridor, withdrawal score and dose and duration of sedative agents with the use of protocolized sedation using COMFORT B scale.

Protocolized sedation with use of various objective scales need to be established and individualized in every PICU based on the age and various diagnostic groups admitted. Further randomized control trials, multicentric studies will be needed to conclusively establish the benefit of protocolized sedation over non protocolized sedation in both homogenous and heterogenous groups of mechanically ventilated children in PICU. Follow up studies can be done to see the effect of protocolized sedation in comparison to NPS group on the cognition and brain development of children.

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APPENDIX-1

PARTICIPANT INFORMED CONSENT FORM (PICF)

(English)

Protocol / Study number: _____

Participant identification number for this trial: _____

Title of project: 'Comparison of Protocolized sedation utilizing the COMFORT –B scale versus non-protocol-directed sedation in mechanically ventilated children'

Name of Principal Investigator: Dr Pujitha Vallabhaneni **Tel.No-** 9618221731

The contents of the information sheet dated that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

The nature and purpose of the study and its potential risks / benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS, Jodhpur. I give permission for these individuals to have access to my records.

I agree to take part in the above study.

---------- Date:

(Signatures / Left Thumb Impression) Place:

Name of the Participant: _____

Son / Daughter of:_____

Complete postal address: _____

This is to certify that the above consent has been obtained in my presence.

Signatures of the Principal Investigator Date:

Place:

1) Witness – 1 2) Witness – 2

Signatures Signatures

Name: Name:

Address: Address:

मरीज़ के लिए सूचित सहमति फार्म

प्रोटोकॉल / अध्ययन संख्या: _____

इस परीक्षण के लिए प्रतिभागी की पहचान संख्या: _____

परियोजना का शीर्षक: सांस लेने के लिए इस्तेमाल की जाने वाली मशीन पर बच्चों में गैर-प्रोटोकॉल-निर्देशित बेहोश करने के लिए कम्फर्ट बी स्केल पैमाने का उपयोग करके प्रोटोकॉलबद्ध बेहोश करने की तुलना

प्रधान अन्वेषक का नाम: डॉ। पूजिता वल्लभानेनी Tel.No- 9618221731

उपलब्ध कराई गई सूचना पत्र की सामग्री को मेरे द्वारा ध्यान से पढ़ा गया है / मुझे विस्तार से समझाया गया है, जिस भाषा में मैं समझता हूं, और मैंने सामग्री को पूरी तरह से समझ लिया है। मैं पुष्टि करता हूं कि मुझे सवाल पूछने का अवसर मिला है।अध्ययन की प्रकृति और उद्देश्य और इसके संभावित जोखिम / लाभ और अध्ययन की अपेक्षित अवधि, और अध्ययन के अन्य प्रासंगिक विवरण मुझे विस्तार से बताए गए हैं। मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और मैं बिना किसी कारण के किसी भी समय वापस लेने के लिए स्वतंत्र हूं, बिना मेरी चिकित्सा देखभाल या कानूनी अधिकार प्रभावित हुए बिना।

मैं समझता हूं कि इस शोध में मेरी भागीदारी और मेरे किसी भी मेडिकल नोट के वर्गों के बारे में मेरे द्वारा एकत्रित जानकारी को एम्स, जोधपुर के जिम्मेदार व्यक्तियों द्वारा देखा जा सकता है। मैं इन व्यक्तियों को अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं।

मैं उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूं।

---------- दिनांक:

(हस्ताक्षर / बाएं अंगूठे का निशान) जगह:

प्रतिभागी का नाम: _____

माता /पिता: _____

पूरा पता: _____

यह प्रमाणित करना है कि मेरी उपस्थिति में उपरोक्त सहमति प्राप्त हुई है।

प्रधान अन्वेषक के हस्ताक्षर दिनांक:जगह:

1) गवाह - 1

2) गवाह - 2

हस्ताक्षर

हस्ताक्षर

नाम

नाम:

पता

पता:

APPENDIX-2

PARTICIPANT INFORMATION SHEET (PIS)

Title of the Study: Comparison of Protocolized sedation utilizing the COMFORT –B scale versus non-protocol-directed sedation in mechanically ventilated children

i) Aims and purpose of the research

Your child is being mechanically ventilated and is currently sedated. We want to evaluate the adequacy of sedation. If required sedation will be increased or decreased based on the evaluation so as to maintain adequate sedation.

Procedure

The child will be enrolled into the study. The initial assessment shall include recording of relevant base line data regarding the child. Using COMFORT B scale, he will be assessed every 4^{th} hourly throughout the period that he has been sedated for mechanical ventilation. Based

on the score on the scale his sedation will be titrated. We will also take data regarding the drug usage and withdrawal effects.

ii) Expected duration of the subject participation- as long as child is sedated

iii) **The benefits to be expected from the research to the subject or to others:**

Our algorithm based approach will save unnecessary over sedation or under sedation in mechanically ventilated children.

iv) **Any risk to the subject associated with the study:** Potentially none.

v) **Maintenance of confidentiality of records:** The medical records of the patient shall be kept confidential and accessed only by the treating physician or, if necessary, by the Ethics Committee of the All India Institute of Medical Sciences, Jodhpur.

vi) **Provision of free treatment, compensation for research related injury:** Not applicable

vii) **Freedom of individual to participate and to withdraw from research at any time without penalty or loss of benefits to which the subject would otherwise be entitled:** You are free to participate in and withdraw from this study at any time you so desire. This will in no way affect your ongoing treatment at the Institute.

viii) **Costs and source of investigations, disposables, implants and drugs:** Drugs used for sedation mentioned are available in AIIMS, you are not expected to pay for these.

ix) **Telephone number/contact number of Principal Investigator and Co investigator:** In case of any concerns related to the study, you should contact:

Dr Pujitha Vallabhaneni, Resident,

All India Institute of Medical Sciences, Jodhpur, Rajasthan 342005;Phone 9618221731

x) It is certified that translation to vernacular is accurate.

रोगी सूचना पत्र (पीआईएस)

अध्ययन का शीर्षक: सांस लेने के लिए इस्तेमाल की जाने वाली मशीन पर बच्चों में गैर-प्रोटोकॉल-निर्देशित बेहोशी के लिए कम्फर्ट बी स्केल स्केल का उपयोग करते हुए प्रोटोकॉल बेहोशी की तुलना

i) अनुसंधान का उद्देश्य

आपका बच्चा वेंटिलेटर पर है। जिसके लिए बच्चे को दवाई दी गई है। कम्फर्ट बी स्केल के आधार पर, नींद की गहराई को तौला और बढ़ाया या घटाया जाएगा ताकि पर्याप्त नींद बनी रहे।

प्रक्रिया

बच्चे को अध्ययन में नामांकित किया जाएगा। प्रारंभिक मूल्यांकन में बच्चे के संबंध में प्रासंगिक आधारभूत डेटा की रिकॉर्डिंग शामिल होगी। कम्फ़र्ट बी स्केल का उपयोग करके हर 4 घंटे में उनका परीक्षण किया जाएगा। पैमाने पर स्कोर के आधार पर उनकी नींद की दवा को बढ़ाया या घटाया जाएगा। हम दवा के उपयोग और वापसी प्रभावों के बारे में भी जानेंगे।

ii) विषय भागीदारी की अपेक्षित अवधि - जब तक बच्चा नींद की दवा पर है।

iii) विषय या अन्य से अनुसंधान से अपेक्षित लाभ: हमारा एल्गोरिथ्म-आधारित दृष्टिकोण यांत्रिक रूप से हवादार बच्चों में अधिक या कम गहरी नींद से बेहोश होने से बचाएगा।

iv) अध्ययन से जुड़े विषय पर कोई जोखिम: संभावित रूप से कोई नहीं।

v) अभिलेखों की गोपनीयता का रख-रखाव: रोगी की चिकित्सा संबंधी अभिलेख केवल तभी आवश्यक हो सकते हैं जब आचार समिति या अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर के उपचार चिकित्सक के साथ आवश्यक हो।

vi) मुफ्त इलाज का प्रावधान, अनुसंधान से संबंधित चोट के लिए मुआवजा: लागू नहीं

vii) किसी भी समय दंड या हानि के बिना अनुसंधान से भाग लेने या वापस लेने के लिए व्यक्ति की स्वतंत्रता: आप किसी भी समय इस अध्ययन से भाग लेने और वापस लेने के लिए स्वतंत्र हैं। यह किसी भी तरह से संस्थान में आपके चल रहे उपचार को प्रभावित नहीं करेगा।

viii) लागत और जांच का स्रोत, डिस्पोजल, इम्प्लांट और ड्रग्स: एआईआईएमएस में नींद की दवाएं उपलब्ध हैं, आपको उनसे भुगतान करने की उम्मीद नहीं है।

ix) टेलीफोन नंबर / प्रधान अन्वेषक और सह-अन्वेषक का संपर्क नंबर: अध्ययन से संबंधित किसी भी चिंता के मामले में, आप निम्न हैं:

डॉ। पूजिता वल्लभानी; निवासी: अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर, राजस्थान 342005; फोन 9618221731

APPENDIX-3

CASE RECORD FORM

COMPARISON OF PROTOCOLIZED SEDATION UTILIZING THE COMFORT –B SCALE VERSUS NON-PROTOCOL-DIRECTED SEDATION IN MECHANICALLY VENTILATED CHILDREN

Enrollment number	
UHID	

Part A: Demographic Details		
S. No.	**Items**	**Response**
1.	Name	
2.	Age	
3.	Gender	
4.		

	Address											
	Pin code											
5.	Contact numbers	Landline										
		Mobile 1										

Part B: Baseline details	
Diagnosis	
Category:	
Cardiac	
Hemato-oncology	
Respiratory	
Postoperative patients	
PIM 3 score	
Ionotropes used	

Part C: Sedation			
Drugs used	Mean daily dose	Cumulative dose	No of days of exposure
Fentanyl			
Dexmedetomidine			
Midazolam			
Ketamine			
Clonidine			

No of sedative classes used	
Neuromuscular blockade to manage agitation (drug and no of days used)	

PART D: Outcome	
Duration of mechanical ventilation	
Duration of PICU stay	
Duration of hospital stay	
PICU discharge status:	
• Mortality (yes/no)	
• Survived	
• Transferred to another hospital	
No of self extubation episodes	
No of extubation failures (reintubations within 24 h)	
No of accidental removal of invasive lines	
No of incidences of reintubations	
VAP (yes/no)	
Catheter associated blood stream infection (yes/no)	
Immobility related stage ≥2 pressure ulcer (yes/no)	
Tracheostomy required (yes/no)	
Delirium (yes/no)	
Study days awake and calm	
Days to first awake calm state	

Study days with pain score <4	
Study days with pain score >4	
Withdrawal symptoms	
Iatrogenic withdrawal syndrome (WAT score ever ≥3)	
Peak WAT score	
Study days with WAT 1 score ≥3	
Time required for weaning	
Post extubation stridor (yes/no)	

FLACC scale

Behavioral Observation Pain Rating Scale

Categories	Scoring		
	0	1	2
Face	No particular expression or smile; disinterested	Occasional grimace or frown, withdrawn	Frequent to constant frown, clenched jaw, quivering chin
Legs	No position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No crying (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or talking to. Distractable	Difficult to console or comfort
Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between 0 and 10.			

Numeric Rating Scale

Wong-Baker FACES® Pain Rating Scale

WITHDRAWAL ASSESSMENT TOOL VERSION 1 (WAT – 1)

Patient Identifier														
		Date:												
		Time:												
Information from patient record, previous 12 hours														
Any loose /watery stools	No = 0 Yes = 1													
Any vomiting/wretching/gagging	No = 0 Yes = 1													
Temperature > 37.8°C	No = 0 Yes = 1													
2 minute pre-stimulus observation														
State	SBS[1] ≤ 0 or asleep/awake/calm = 0 SBS[1] ≥ +1 or awake/distressed = 1													
Tremor	None/mild = 0 Moderate/severe = 1													
Any sweating	No = 0 Yes = 1													
Uncoordinated/repetitive movement	None/mild = 0 Moderate/severe = 1													
Yawning or sneezing	None or 1 = 0 ≥2 = 1													
1 minute stimulus observation														
Startle to touch	None/mild = 0 Moderate/severe = 1													
Muscle tone	Normal = 0 Increased = 1													
Post-stimulus recovery														
Time to gain calm state (SBS[1] ≤ 0)	< 2min = 0 2 - 5min = 1 > 5 min = 2													
Total Score (0-12)														

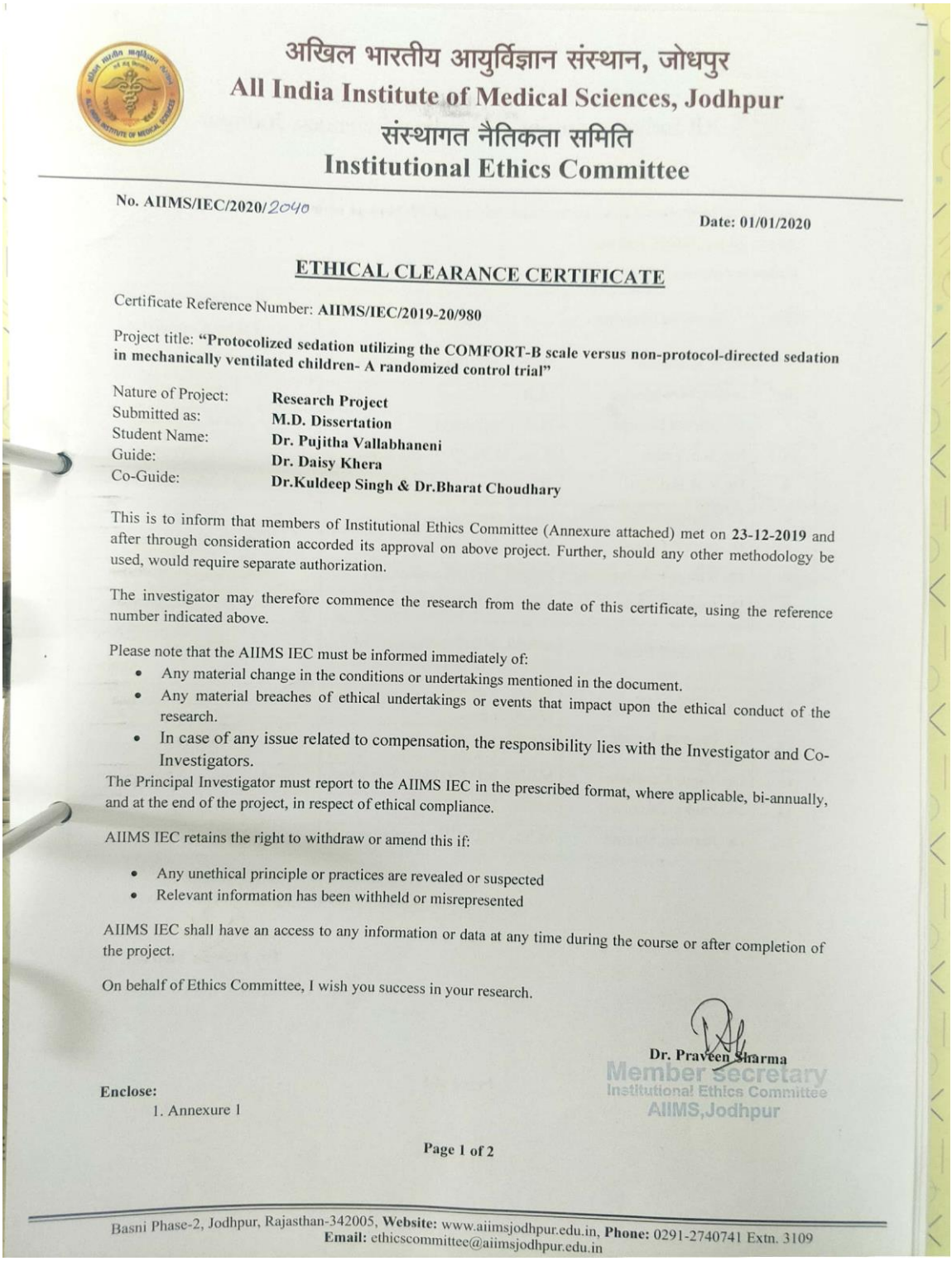
COMFORT B Scoring

date	Day of ventilation	8am	12pm	4pm	8pm	12am	4am

Appendix 1 - Comfort-B scale

Level of consciousness: alert	
Deep sleep	1
Light sleep	2
Lethargic	3
Awake and alert	4
Hyper-alert	5
Calmness / Agitation	
Calm	1
Slightly anxious	2
Anxious	3
Very anxious	4
Panicky	5
Respiratory response (only if patient is under mechanical ventilation)	
Absence of coughs and of spontaneous breathing	1
Spontaneous respiration with little or no response to ventilation	2
Coughs or occasional resistance to the ventilator	3
Active breathing against the ventilator or regular coughs	4
Fights ventilator, coughs	5
Crying (only if patient is breathing spontaneously)	
Quiet breathing, no crying sounds	1
Mumbling/ whimpering	2
Whining (monotonous sound)	3
Crying	4
Screaming	5
Physical movement	
Absence of movement	1
Occasional slight movements	2
Slight frequent movement	3
Vigorous movement restricted to the extremities	4
Vigorous movement including head and chest	5
Muscular tone	
Totally relaxed	1
Reduced muscle tone	2
Normal muscle tone	3
Increased muscle tone with flexion of fingers and toes	4
Extreme rigidity with flexion of fingers and toes	5
Facial tension	
Facial muscles totally relaxed	1
Normal facial tone, without evident tension	2
Evident tension of some facial muscles	3
Evident tension of the whole face	4
Contorted facial muscles	5

APPENDIX - 4



अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2020/2040

Date: 01/01/2020

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2019-20/980**

Project title: **"Protocolized sedation utilizing the COMFORT-B scale versus non-protocol-directed sedation in mechanically ventilated children- A randomized control trial"**

Nature of Project:	**Research Project**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Pujitha Vallabhaneni**
Guide:	**Dr. Daisy Khera**
Co-Guide:	**Dr.Kuldeep Singh & Dr.Bharat Choudhary**

This is to inform that members of Institutional Ethics Committee (Annexure attached) met on **23-12-2019** and after through consideration accorded its approval on above project. Further, should any other methodology be used, would require separate authorization.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.
- In case of any issue related to compensation, the responsibility lies with the Investigator and Co-Investigators.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Enclose:
1. Annexure 1

Page 1 of 2

Basni Phase-2, Jodhpur, Rajasthan-342005, **Website:** www.aiimsjodhpur.edu.in, **Phone:** 0291-2740741 Extn. 3109
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