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Practice guidelines for sedation and analgesia management in the PICU: A feasibility and acceptability trial.

Authors:

Samantha J Keogh [1,3] RN PhD, Debbie A Long [2,3] RN PhD, Desley V Horn [2] RN MSc

[1] Nursing Research Services, Royal Children's Hospital, Brisbane, Queensland, Australia

[2] Paediatric Intensive Care Unit, Royal Children's Hospital, Brisbane, Queensland, Australia

[3]NHMRC Centre of Research Excellence in Nursing (NCREN) - Centre for Health Practice Innovation – Griffith Health Institute, Griffith University, Nathan, Australia

c/- NHMRC Centre of Research Excellence in Nursing

Griffith University, Nathan Campus

170 Kessels Road

Brisbane Qld AUSTRALIA 4111

Tel: +61 7 3735 4886

Fax: +61 7 3735 3560

Email: s.keogh@griffith.edu.au

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Abstract

Objectives: The aim of this study was to develop, implement and evaluate guidelines for sedation and analgesia management in the paediatric intensive care unit (PICU) as a prelude to future trial work.

Setting: The guidelines were trialled in two paediatric intensive care units at different hospitals in an Australian metropolitan city.

Participants: Patients admitted to the PICU and ventilated for ≥24 hours, aged more than one month of age and not admitted for seizure management or terminal care were recruited into the study.

Intervention: A trial of guidelines for sedation and analgesia management for critically ill children including algorithm and assessment tools.

Primary and secondary outcome measures: In addition to key outcome variables (ventilation time, medication dose and duration, length of stay), feasibility outcomes data (recruitment, data collection, safety) were evaluated. Guideline adherence was assessed through chart audit and staff were surveyed about merit and use of guidelines.

Results: The guidelines were trialled for a total of 12 months on 63 patients and variables compared to control group (n= 75). Analysis demonstrated significant differences in median Morphine infusion duration between groups (3.63 vs 2.83 days, *p=0.05*) and maximum doses (120 vs 97.5 mcg/kg/hr) with no significant difference in ventilation duration. Chart audit revealed varied use of tools, but staff were positive about the trial and the perceived impact the guidelines had on practice.

Conclusions: The sedation guidelines in this study appear to be feasible in practice, and impacted on the duration and dosage of agents without adversely impacting on ventilation duration or length of stay. The results of the study could inform future trial work in this area.

Strengths of study:

- Detailed outline of guideline development process based on consensus paper and available evidence
- Original dual site feasibility (pilot) study testing impact of guidelines on patient, quality and practice outcomes
- Generation of clinical and trial process data to inform future trial work

Limitations of study

- No firm evidence or 'cause and effect' can be concluded due to pre/post study design and small sample size

Introduction & Background

Sedation and analgesia are necessary components in the care of all critically ill patients, especially those requiring mechanical ventilation. The main indications for their use include: to reduce patient pain, anxiety and agitation, induce amnesia, facilitate mechanical ventilation, prevent the displacement of endotracheal tubes, and decrease cellular metabolism [1-3]. The detrimental impact of poor sedation practices in intensive care units has increasingly become a focus for researchers and clinicians and extends from concerns for both under sedation to over sedation[4]. Both under and over sedation has the potential to lead to agitated patients with compromised short term safety issues and long term psychological recovery[5 6]. The consequences of prolonged use of sedative and analgesic agents in the intensive care unit patient include central nervous system activation, gastrointestinal disturbances, and sympathetic hyperactivity. These signs and symptoms have been related to tolerance and withdrawal phenomena and also hold implications for the patient's physical and psychological well being as well as health care costs [7-9]. These risks are potentially amplified in the critically ill child in the paediatric intensive care unit (PICU) due to the developing brain[10 11].

The 2006 consensus guidelines on sedation and analgesia in critically children established a standard for clinical practice in paediatric intensive care units (PICU) [12]. The guidelines' key recommendations include advice on a loading dose and administration for analgesia and sedation medication, the use of validated pain and sedation assessments tools, withdrawal assessment, and the inclusion of non-pharmacological interventions. Surveys of sedation and analgesia management in PICUs have identified a lack of specific protocols for sedation and analgesia management [13-15]. This research has also highlighted wide variations in physician practice, nursing assessment, pharmacological agents, as well as administrative methods and doses. Limited use of assessment tools has also been reported, and there were no measurements or guidelines for withdrawal of drugs.

A number of studies have attempted to evaluate the impact of sedation and analgesia guidelines in PICU, however the results have been varied. Prior to the publication of 2006 Consensus guidelines for critically ill children a Canadian PICU evaluated the impact of a sedation and analgesia protocol on patient outcomes [16]. This protocol centred on the use of a treatment algorithm prescribing the titration of medication to achieve a desired pain and sedation assessment score. The study was limited to a secondary quality assurance evaluation of a small purposive sample (n=10) from a larger parent study of a sedation tool. Results of the study showed that patients received higher doses of Fentanyl (428 ug/kg vs 32ug/kg) and Midazolam (12228 ug/kg vs 9740ug/kg) while on the protocol. No difference in the number of bolus treatments between groups was reported. The focus of assessment was on level of patient sedation. The researchers believed that patients' sedation and pain levels were underestimated pre study and that the observed increase in medication, was associated with less risk of under sedation. Data on ventilation time or length of stay was not provided.

Similarly, a pre/post study of a sedation and analgesia protocol in a Dutch PICU resulted in a significant increase in medication administration [17]. Morphine dosage increased from 6.9mcg/kg/hr to 11.2mcg.kg.hr (p=0.004) and Midazolam dosages increased from 54mcg/kg/hr to 112.8 (p= 0.0001). A simultaneous increase in the proportion of patients deemed adequately sedated as evaluated by the COMFORT scale increased from 63% pretest to 72% posttest. Again, no comment or data on ventilation time or length of stay was provided to evaluate impact of increased sedation on these parameters.

Conversely, Deeter and colleagues (2011) demonstrated a potential reduction in medication following the implementation of a sedation and analgesia protocol [18]. The researchers used a retrospective cohort study design and analysis revealed a reduction in Morphine infusion duration (6 days vs 5 days, p=0.015) and Lorazepam infusion duration (2 days vs 0 days, p<0.001). Actual dosages were not captured in the study so a reduction in medication

administration can only be implied. A corresponding reduction in ventilation days and length of stay was also reported in the intervention group. This reduction in sedation was not associated with an increase in accidental extubation with rates at 0.32/100 ventilator days pretest and then at 0.23/100 ventilators posttest.

A Korean study also reported a reduction in medication administration related to the implementation of protocol [19]. Median Fentanyl doses decreased from 495.5mcg/kg/hr 204mcg/kg/hr (p=0.02) and median Midazloam doses decreased from 55mcg/kg.hr to 37.5mcg/kg.hr (p=0.08). Duration of ventilation and length of stay was also significantly reduced. No data on other quality assurance indicators (i.e. accidental extubation) were reported. In contrast to the other interventions, which were largely nurse driven physician titrated medication following assessment by the pharmacist and consultation with nursing staff.

In contrast to all aforementioned studies, an Australian study reported that the dosage and administration of the unit's commonly used pharmacological agents (Morphine, Fentanyl and Midazolam) remained constant in the pre and post guideline audit [20]. Actual dosages were not reported. The researchers did note and report, however, a significant reduction in mean infusion dose of Ketamine (3mcg/kg/min 95%CI -0.8—5.2 p=0.01) as well as a reduction in the proportion of patients receiving bolus IV Ketamine doses from 7% to 0% (p=0.003). Conversely the proportion of patients receiving oral Clonidine increased from 14% to 32% (p=0.001). These changes were in line with recommendation of the study guideline. Other changes noted in the study included an increase in the use of a validated sedation and pain assessment tool (up by 19% and 25% respectively) as well as improved documentation of boluses and management plan.

All of the reviewed studies have contributed to our knowledge and understanding of sedation and analgesia management in critically ill children. Differences in guideline specifics, model

of care, and study design may have contributed to the varied outcomes observed in the above studies and limits their ability to inform best clinical practice. The aim of this study was to develop sedation and analgesia management guidelines based on the 2006 consensus recommendations and test their feasibility and acceptability in practice as a prelude to rigorous trial evaluation of guidelines in practice.

Methods

Aims and Objectives of Study

The main aim of this study was to develop, implement and trial locally developed guidelines for sedation and analgesia management. The objectives were to test the feasibility and acceptability of the guidelines in practice.

Study design

This dual site study used a pragmatic pre and post test design to examine the feasibility and impact of the guidelines on patient and practice outcomes. A chart audit was used to assess the level of guideline adherence or adoption and a (nursing) staff survey was conducted to ascertain staff perceptions of guideline utility and acceptability in practice. The study received full ethical and institutional approval (HREC/05/QRCH/19).

Setting

The study units were two eight-bed PICUs located at tertiary referral children's hospitals admitting patients from 0-16 years of age with a range of diagnoses. Post registration qualifications in either paediatrics, ICU or PICU were held by approximately 48% of the nursing staff.

Participants

The target population was all patients ventilated for ≥ 24 hours within the PICU, aged more than one month of age and not admitted for seizure management or terminal care. All eligible

patients were consecutively enrolled into the study. As the main aim of the study was feasibility rather than hypothesis testing, the statistical power of the sample was of reduced importance. Nonetheless, a sample size calculation was conducted based on the main quality control variable of total ventilation time. The figures were drawn from a local retrospective analysis, as there is no normative reference for ventilated paediatric patients. To be able to detect a difference of 24 hours with a Type I error of 5% (two tailed) and 80% power a sample of at least 75 patients were required in each arm. Eligible patients were consecutively enrolled into the study.

Guideline development

The guidelines for this study were developed around an algorithm for each of the identified phases of sedation (See Appendix 1). The key recommendations of these guidelines were based on the same key recommendations in the 2006 consensus paper and summarised in Table 1 [12].

INSERT TABLE 1 Summary of consensus guidelines.

A range of non pharmacological strategies to minimise patient stress and pain, and optimise comfort are supported by varying levels of evidence ranging from case studies to Cochrane systematic reviews. These were not new strategies but it was important to incorporate them into the guidelines to promote a holistic approach to pain and sedation management and reflect the recommendations of the consensus guidelines. Strategies recommended were aimed at moderating the PICU environment where possible (i.e. minimising high intensity light and noise, ensuring rest periods) [21 22]; minimising discomfort of invasive devices; regular repositioning and limb support with pillows, pressure relieving devises or swaddling [23 24]; monitoring and optimising hydration, nutrition and essential cares (e.g. oral and eye care); supporting parental visitation and reassurance as well as therapeutic (non-technical) touch [25 26].

New assessment scales for behavioural state, pain and withdrawal assessment were integral to the guidelines. These included the State Behaviour Scale (SBS)[27 28], the Multidisciplinary Assessment of Pain Scale (MAPS)[29-32] and the Opioid Benzodiazepine Withdrawal Assessment Scale (WAS) [33 34].

The three phases of sedation (acute, plateau and weaning) management were derived from patterns observed in a retrospective audit conducted earlier by the research team [35 36] and from the literature [9 12 37-39]. The guidelines reflect the dynamic nature of a PICU patient's admission and allow for movement between and within phases according to patient need, response and condition.

As the main aim of the guidelines was to improve consistency in medication practices, it was vital to get a consensus on prescribing practices within the study units. Even the authors of the consensus guidelines note that there is limited evidence to draw on and the recommendations were based on knowledge of drug pharmacokinetics, case study reports, expert opinion, and also the understandings of pain management, drug tolerance and withdrawal medicine. Morphine and Midazolam are the most common analgesic and sedative agents used in PICUs [3 14 40 41] and the drugs of choice in the study units. They are typically used in combination as together they have a synergistic effect that often allows for use of lower doses. Midazolam doses can be reduced as much as 30%-50% when combined with an opioid [42]. Nonetheless, prolonged and/or heavy sedation persists in critical care units, and as a result tolerance and withdrawal syndrome complicate recovery.

In the Acute Phase the guidelines proposed a significant loading dose to achieve the desired analgesia and sedation goals, followed by regular patient assessment and incremental medication changes to achieve and maintain these goals. If the maximum dose allowed was reached (i.e. 300mcg/kg/hr for past 4 hours) then use of adjunct or alternative drugs was

recommended (i.e. clonidine, fentanyl). “Drug cycling” has been reported to be helpful in the United Kingdom, where 25% of PICUs surveyed reported rotation of sedatives to minimize tolerance [3]. In another paper, consultant intensivists conducted biweekly chart reviews of each patient in the ICU and regularly change their sedation regimens [43]. Although these authors imply success with drug tolerance, no numerical data was offered in support.

Once in the Plateau phase, the key change in practice was the recommended conversion from intravenous to long acting enteral agents. This approach is based on the principles of narcotic withdrawal where withdrawal syndrome is managed by conversion to an orally active drug with a longer half life (such as methadone or diazepam) that has a more steady state serum concentration, more readily facilitating a slow taper of the drug and minimizing the severity of withdrawal symptoms or even development of withdrawal syndrome [44-47]. The advantages of methadone are an oral bioavailability of 75% to 80% allowing for oral administration, and a prolonged half-life of 12-24 hours, allowing twice daily administration (ibid). There is a general reluctance to use diazepam for critically ill patients because of its long elimination and concerns about excessive and prolonged sedation. However, similar to methadone, diazepam’s long acting active metabolites theoretically should result in small changes in serum drug concentrations and may decrease fluctuations in sedation state and therefore be a more appropriate agent for long term sedated patients [39].

The formal acknowledgement of a Weaning phase with a dedicated assessment tool and weaning regime was new practice for the study units. No validated opioid or benzodiazepine weaning schedule was found however a consensus of opinion across the literature supports daily reduction of 5% to 10% or an initial reduction of 20% to 40% and followed by a 10% reduction once or twice daily, depending on patient response [39 48]. The protocol for weaning incorporated into these guidelines approximated these recommendations.

Guideline Implementation

The guidelines encompassed many changes in practice: new assessment scales, standardising of practice, conversion to oral agents, algorithms, and a discreet weaning pathway. In the interest of maximising staff understanding and uptake of the tools, a phased implementation process was adopted with the gradual introduction of each tool into the units, followed by orientation and implementation to the algorithm phases and medication administration. Staff in-services introducing the study and guidelines were held over an initial fortnight with phased introduction and implementation of each assessment tool over the following months. These were further supported by bedside education on tool use and supplemented by information and teaching aids on the units' computer system.
In practice, the PICU team set sedation and analgesia goals as part of the daily patient review and staff at the bedside (usually nurses) used the guidelines to achieve the set goals.

Outcome variables

Data was collected from all eligible patients over 12 months (6 months historical control and 6 months post implementation), plus of a break for the implementation period. In addition to the main study outcomes, the pilot study collected outcomes to establish feasibility of the protocol and processes. Feasibility data outcomes included the success of screening and recruitment strategies; tested data collection and entry processes; confirm required costs for Research Nurse time, and produce further estimates of ventilation times and medication dosing, that can be used to finalise sample size requirements for the larger trial, and inform funding applications for same. The main study outcomes measured included total ventilation time (TVT), sedation doses and duration, length of stay in the PICU (LOS), plus quality indicators such as, accidental extubation and readmission rates. Potentially confounding variables collected included patient age, gender, diagnosis, and the Paediatric Index of Mortality (PIM2) as a measure of acuity. Nurses in the study setting routinely collect and record standard demographic and biophysiologic patient measurements on the local computerised information system. The revised paediatric index of mortality (PIM2) is a simple model of mortality in paediatric intensive care based on admission data and uses ten

explanatory variables [49]. Guideline fidelity was measured through chart review using an audit tool based the 19 key components of the guidelines. Staff perceptions were ascertained through administration of a researcher developed survey with questions on ease of use, impact on practice, perceived benefit, facilitation of team management, and promotion of nurse autonomy at bedside. Staff members were also given the opportunity to comment on strengths and limitations of the guidelines.

Statistical Analysis

Data were analysed using PASW 18.0 (SPSS Inc.). Descriptive statistics were used for demographic data. Continuous values reported were medians and ranges due to the large spread of the data. Categorical variables were reported as counts and percentages. Non parametric Mann Whitney or Cross tabulation and Pearson's Chi Square were performed to compare groups. The probability of remaining ventilated between groups was analysed using survival analysis. Adherence to guidelines was reported in counts and percentages. The influence of diagnostic group on guideline adherence was analysed using Pearson's Correlation and comparison of means using student's T-test. Survey responses were reported in counts and percentages as well as significant themes derived from qualitative data.

Results

During the two study periods (12 months each) 173 and 235 patients were ventilated in the respective pre and post guideline implementation periods. After screening for eligibility 75 and 70 patients were enrolled into the pre and post groups. Some patients were lost to the study in the intervention group because of deviation from research protocol, major deviations from the guidelines, one group of parents did not consent to use of the drugs, and transfer to another hospital. Ultimately there were 75 in the control group and 63 in the post implementation group. Data were analysed on a per protocol basis. Figure 1 demonstrates the sampling framework and exclusion criteria.

INSERT FIGURE 1

Table 2 shows the main characteristics measured for each sample. Both groups were comparable with no significant differences between age, weight, sex, or reason for admission. There were also no significant differences identified between the TVT and LOS for each group. There were no incidents of accidental extubation or readmission within 48 hours for subjects in either group for the study.

Table 3 shows the different drug characteristics between groups, demonstrating a greater variance in drug usage. The decrease of 19 hours in the median infusion time of Morphine between groups approached significance (87hrs vs 68 hrs, $p=0.059$). There were changes in the median minimum and maximum Morphine doses, though not significantly. A reduction of 11 hours was identified with median infusion of Midazolam between groups, however this difference was not significant. Significant changes in the median minimum and maximum doses of Midazolam were observed (MIN 10mcg/kg/hr vs 17 mc/kg/hr, $p<0.001$ and MAX 120mcg/kg/hr vs 180mcg/kg/hr, $p<0.001$).

INSERT TABLES 2 & 3

Applying the Kaplan-Meier curve of risk to the probability of remaining ventilated to each group demonstrated that the protocol directed group did not have an increased risk of remaining ventilated (see Figure 2). The probability of remaining ventilated was reduced in the intervention group (by just less than a day at 21 hours); however this was not statistically significant.

INSERT FIGURE 2

Other significant changes in practice were the greater use of adjunctive and alternative medication, in particular methadone. Results showed that prior to the guideline implementation there was limited use of alternative medications (1-2 alternative medications or even none). Post guideline implementation the numbers of alternative medications used increased. More detailed analysis revealed a significant difference with the use of Methadone pre 3% - post 33% *p<0.001;* Diazepam pre 5% - post 25%, *p=0.001;* Chloral Hydrate pre 32% - post 58% *p=0.002;* Propofol pre 60% - Post 20% *p<0.001;* and Neuromuscular blockade agents pre 60% - post 47.6% *NS.*

Chart Audit

Sixty-three charts from the post implementation period were reviewed to identify if staff had followed at least 75% of the 19 key components of the guidelines and quantify the level of assessment and scoring. Overall adoption was achieved in 23 (36%) of the charts audited. Separate analysis within each of the phases demonstrated that adoption was achieved in 30 (47.6%) in the acute phase, 23 (36.5%) in plateau, and 25 (39.7%) in the weaning phase. Pain and sedation scores were assessed and documented in 95% (n=60) of charts in the acute and plateau phases, and 85% (n=54) of charts in the weaning phase. The withdrawal score was assessed and documented appropriately in 75% (n=47) of charts.

Staff survey

The response rate was 49% (n=54). Participants' responses were divided into four categories: awareness/use, strengths, limitations and suggestions for improvement. Fifty-two (96%) staff regularly referred to the guideline to assist with decision making and to provide prompts and cues. There appeared to be some confusion as to who was primarily responsible for the initiation of the guidelines, with 12(23%) suggesting is was the consultants' responsibility and 32(60%) stating it was the bedside nurse. Table 4 outlines further responses.

INSERT TABLE 4

Perceived strengths of the tool included the structured nature of the guidelines, promotion of consistency in practice and the resulting increased awareness regarding sedation management. Conversely perceived limitations included the perceived complexity of algorithm, confusion with delineation and movement between phases, and the lack of accommodation of increased drug tolerance with long term patients. Staff suggested simplifying the algorithm and using larger print, incorporating recommendations for short term patients and providing clinical example as guides. . Table 5 provides the staff comments on perceived strengths and weaknesses of the guidelines Overall four major themes were expressed by study participants (see table 5): (1) a knowledge deficit about some aspects of the guidelines, (2) high value placed on individualised patient care, (3) perceived ineffectiveness of the guidelines for some patients, and (4) disagreement between doctors and nurses on responsibilities.

INSERT TABLE 5

Discussion

This pragmatic study demonstrated that the guidelines were feasible and acceptable in practice. The use of guideline directed sedation and analgesia management allowed the PICU team to achieve the patient's sedation goals quicker without significantly increasing ventilation times or PICU length of stay. Full adoption of all aspects of guidelines was not realised but results demonstrated improved levels of patient assessment, increased use of enteral agents, and largely positive feedback on guidelines in practice.

The observed increases in median minimum and maximum doses of Morphine and Midazolam do not seem to have increased patient TVT or LOS, and in fact the duration of each infusion was reduced, significantly in the case of Morphine. It would appear that the

PICU team could reach the sedation goals quicker without compromising the patient. The results of Kaplan-Meier Risk analysis demonstrate that there was reduced risk of remaining ventilated in the post-test group though this was not statistically significant. However, a median difference of 21 hours between groups may be viewed as clinically significant if it is related to early extubation and/or discharge.

The guidelines and implementation process in this study also appear to have significantly increased awareness and usage of alternative medications to complement or replace the Morphine/Midazolam. This was particularly evident with the use of Methadone and Diazepam. Use of Methadone rose from 3% pre intervention to 33% post intervention. Use of Diazepam rose for 5% pre intervention to 25% post intervention. One of the key recommendations to emerge from the literature and therefore included in the guidelines was the transition from continuous intravenous analgesia and sedation to regular oral agents. Prolonged administration of opioids and benzodiazpines may result in the development of drug tolerance and then withdrawal syndrome if these agents are abruptly discontinued [9 38 50 51]. Research has shown that this can be prevented by slowly tapering the intravenous administration of the drug or switching from intravenous morphine and midazolam to orally active drugs with a longer half-life, such as methadone and diazepam [45 47]. In general the increased use of adjunct medication demonstrated the heightened awareness of the appropriate use of complimentary drugs to help the patient reach the required sedation goal in a timely manner.

The chart audit demonstrated that the assessment and documentation of patient's pain and sedation was well recorded reflecting sound staff understanding and uptake of the new assessment tools. The adoption score for the withdrawal phase was the lowest of the three phases, which may have resulted from less familiarity and knowledge with the tool and phase. This is consistent with findings were found in a review of similar studies [52]. Suggested reasons for non-adherence included complexity of guideline or algorithm, staff not

valuing or understanding goal of guideline, perceived redundancy of guideline if staff already competent practitioners in this area (ibid). Potential solutions to these issue included ongoing staff education and timely feedback related to the guideline to continuously reinforce importance, ease of use, and troubleshoot issues[53]. In addition to surveying staff opinion, it is also important to conduct periodic chart audits to quantify guideline fidelity. This will help minimise self-report bias as was somewhat reflected in this study[54]. Staff perceptions of guideline principles and use were positive although level of adherence variable. So the full impact of the intervention was not realised.

In conjunction with the audit, a survey of staff perceptions and attitudes were undertaken to establish if these influenced adoption of the guidelines. In line with other similar studies, staff were largely positive and constructive in their feedback[17 55 56]. All feedback has been utilised to improve the guidelines. Engaging staff and providing feedback during the process of procedural change is a vital step in optimising translation to practice.

The importance of the findings of this study are that they demonstrate that collaborative guidelines for sedation management can optimise the PICU patient's sedation and analgesia management without compromising quality of care (TVT, LOS, quality indicators). The results are similar to those in the adult population where guideline or protocol driven sedation has been linked to a reduction in duration of continuous intravenous sedation, ventilation time and associated health care costs [57-61]. Evaluation of feasibility outcomes has aided in development a realistic plan about participant recruitment, staff education to optimise guideline fidelity, safety of guidelines in clinical practice and collection of key outcome variables.

Implications & Recommendations

No definitive causal effect can be attributed to the guidelines on outcomes due to the pre post study design and small sample size. Conducting the study in two units assists with the

generalisability of the study and its results. Some specifics of the guidelines and algorithm, however, might need modification to reflect local practice. For example, use of different drugs (fentanyl instead of morphine) and different patient populations (post cardiothoracic surgery). The study results are most useful in informing the structure and outcome measures for a follow on clinical trial in this area.

Results from the study, audit and survey have informed changes and modifications to optimise staff understanding and use of sedation guidelines in practice. Weaning from sedation agents and the concept of withdrawal appear to be areas of practice that need more attention. The researchers are trialling and evaluating a revised withdrawal assessment tool and studies examining the impact of different sedative agents are planned also. The study units plan to continue to use the guidelines and tools in their modified form pending the results of larger trial work. The modern ICU is an important focus for quality improvement efforts. Guidelines cannot automatically guarantee improved quality of care; however, they do direct the clinician in the pursuit of this objective.

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Contributorship statement:

All three authors, Samantha Keogh, Debbie Long and Desley Horn meet the key three ICMJE guidelines for authorship with each having made (a) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content; and (c) final approval of the version to be published.

Competing interests

None of the authors have any competing interest or financial disclosure related to this study to declare.

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Data sharing statement

A copy of the guidelines can made available by emailing Debbie.Long2@health.qld.gov.au.

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Figure 1: Sample framework

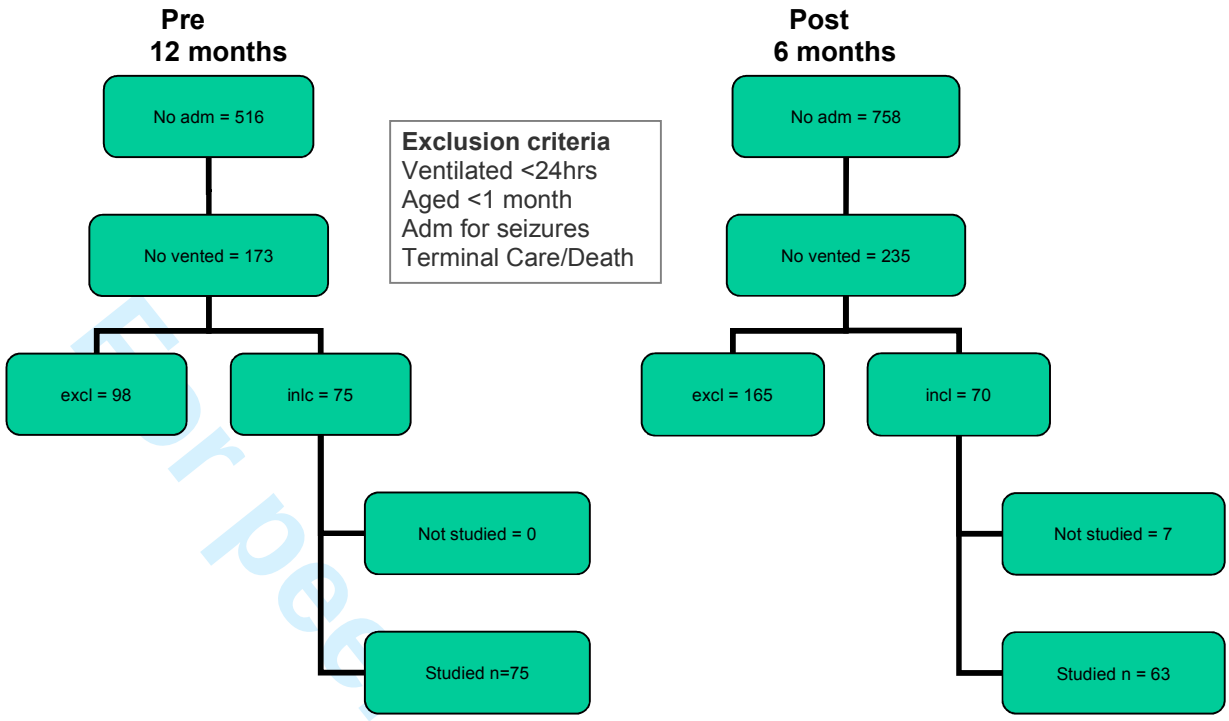

Figure 2: Kaplan-Meier Curve of risk of remaining ventilated between groups

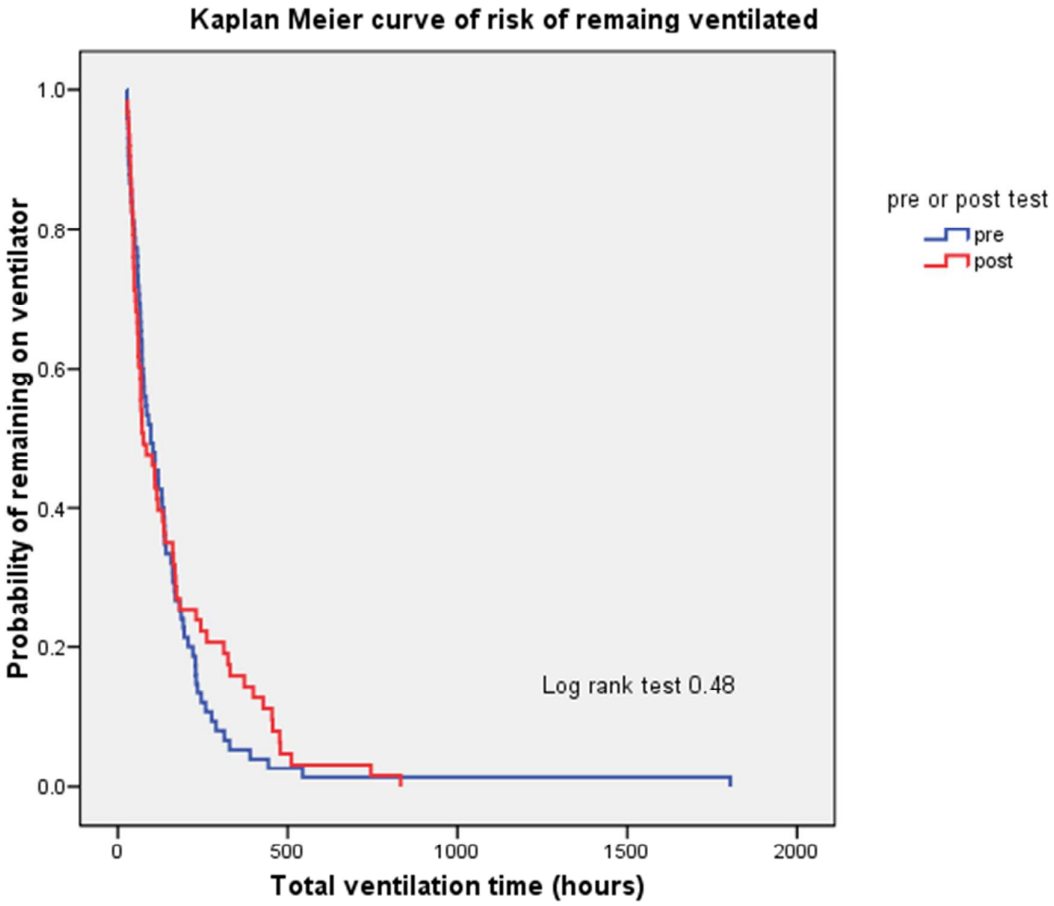

Table 1. Summary of Consensus guidelines (based on Playfor et al 2006)

1. Non pharmacological interventions	i.	Any correctable environmental and physical factors causing discomfort should be addressed alongside the introduction of pharmacological agents.
	ii.	A normal pattern of sleep should be encouraged. Attention should be paid to lighting, environmental noise and temporal orientation of patients.
2. Pain assessment and analgesic management	i.	All critically ill children have the right to adequate relief of their pain. Local and regional anaesthetic techniques should be considered. A patient controlled analgesia (PCA) device may be useful in older children.
	ii.	Pain assessment should be performed regularly by using a scale appropriate to the age of the patient and routinely documented. The level of pain reported by the patient must be considered the current standard of analgesia. Patients who cannot communicate should be assessed for the presence of pain-related behaviours and physiological indicators of pain. A therapeutic plan for analgesia should be established for each patient and regularly reviewed.
	iii.	Recommended pharmacological agents for analgesia include opioids (e.g. Morphine, Fentanyl) for the relief of severe pain, nonsteroidal anti-inflammatory drugs (NSAIDs) for moderately severe pain, and paracetamol for mild to moderate pain.
3. Sedation assessment and recommended or commonly used sedative agents	i.	Adequate analgesia should be provided to all critically ill children regardless of the need for sedation. The use of clinical guidelines for sedation is recommended.
	ii.	The level of sedation should be regularly assessed and documented using a validated and age appropriate sedation assessment scale. The desired level of sedation should be identified for each patient and should be regularly reassessed. Doses of sedative agents should be titrated to produce the desired level of sedation.
	iii.	Recommended pharmacological agents for sedation include Midazolam or Clonidine. Early use of enteral sedative agents (e.g Chloral Hydrate, Promethazine) is recommended. Propofol should not be used to provide continuous sedation in critically ill children.
4. Withdrawal syndrome assessment, prevention and management	i.	The potential for opioid and benzodiazepine withdrawal syndrome should be considered after 7 days of continuous therapy.
	ii.	When subsequently discontinued, the doses of these agents may need to be routinely tapered.

	Pre	*Post*	*Statistic*
Age (yrs) Median (range)	2.08(0.08-15.25)	1.75(0.08-14.25)	NS Mann Whitney
Weight (kgs) Median (range)	11.5(2.3-65)	12(2-60)	NS Mann Whitney
Sex No (%)	Male 45(60%)	Male 38(60%)	NS Chi square
Primary Diagnosis No (%)	Resp 29(39%)	Resp 21(33%)	NS Chi square
PIM Median (range)	5.00 (1-46)	5.20 (1-58)	NS Mann Whitney
TVT(days) Median (range)	4.02(1.1-75.15)	3.12(1-34.7)	NS Mann Whitney
LOS (days) Median (range)	6.3(1.9-180)	5.8(2-36)	NS Mann Whitney

NS = not statistically significant i.e. p≤0.05

Table 2: Baseline characteristics in the study groups

	Control *Median (range)*	*Intervention* *Median (range)*	*Statistics*
Morphine			
Infusion duration (hrs)	87 (24-538)	68 (12-658)	*p=0.059* *- 19hrs*
Min dose (mcg/kg/hr)	10 (2-41)	17 (5-50)	NS + 7mcg/kg/hr
Max dose (mcg/kg/hr)	120 (20-500)	97.5 (20-560)	NS - 22.5 mcg/kg/hr
Midazolam			
Infusion duration (hrs)	71 (10-560)	60 (3-474)	NS - 11hrs
Min dose (mcg/kg/hr)	10 (2-203)	24 (6-100)	*p<0.001* +14 mcg/kg/hr
Max dose (mcg/kg/hr)	120 (21-500)	180 (20-800)	*p<0.001* +60 mcg/kg/hr

NS = not statistically significant i.e. p≤0.05

Table 3: Outcome variable comparison between study groups

Questions	*Yes Response n=54*
The sedation guidelines and flowchart are easy to follow	58.5%
The flowchart facilitates the sedation management process	87%
Patients benefit from having a constructive escalation program	96.3%
Patients benefit from having a constructive titration program	94.3%
Patients benefit from having a constructive weaning program	96.2%
A multidisciplinary approach enhances sedation management	96.3%
The guidelines give me more autonomy in managing sedation	68.5%
The guidelines improve overall sedation management	88.5%

Table 4: Staff perceptions of sedation guidelines in practice

Strengths
▪ The bedside nurse 'knows' the patient and their requirements, can initiate changes, use objective data on the screen, can see changes and ask for review if needed. ▪ It is a clinical tool to justify an increase or decrease in sedation. Allows for uniform/consistent decision making. ▪ Empowers and rationalises nursing changes in sedation. ▪ Everyone using the same guide should translate to more consistent care. There is more autonomy for nurses, particularly with less experienced registrars. It potentially irons out variations in individual consultant preferences. ▪ It has increased the awareness amongst staff and prompts discussion. ▪ It places importance on sedation and assists nurses to provide better sedation. Patients more comfortable equals parents more comfortable.
Limitations
▪ Can be complicated because of the amount of detail. ▪ Needs definitions and differential diagnoses for each of the phases. ▪ Not all patients fit the guidelines or respond as predicted. ▪ Requires full concentration with attention to detail and practice to become familiar. ▪ Lack of medical leadership/ownership shared. ▪ Difficult to continue in ward, particularly with weaning. ▪ Have trouble with some long term patients following the guidelines and keeping them comfortable.

Table 5: Staff perceptions of strengths and limitations of sedation guidelines.

BMJ Open

Practice guidelines for sedation and analgesia management of critically ill children: A pre and post test study evaluating of impact and feasibility in the PICU.

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Practice guidelines for sedation and analgesia management of critically ill children: A pre and post test study evaluating of impact and feasibility in the PICU.

Authors:

Samantha J Keogh [1,3] RN PhD, Debbie A Long [2,3] RN PhD, Desley V Horn [2] RN MSc

[1] Nursing Research Services, Royal Children's Hospital, Brisbane, Queensland, Australia

[2] Paediatric Intensive Care Unit, Royal Children's Hospital, Brisbane, Queensland, Australia

[3]NHMRC Centre of Research Excellence in Nursing (NCREN) - Centre for Health Practice Innovation – Griffith Health Institute, Griffith University, Nathan, Australia

c/- NHMRC Centre of Research Excellence in Nursing

Griffith University, Nathan Campus

170 Kessels Road

Brisbane Qld AUSTRALIA 4111

Tel: +61 7 3735 4886

Fax: +61 7 3735 3560

Email: s.keogh@griffith.edu.au

Keywords: Paediatric Intensive Care, Sedation, Analgesia, Guidelines.

Abstract

Objectives: The aim of this study was to develop, implement and evaluate guidelines for sedation and analgesia management in the paediatric intensive care unit (PICU).

Method: The study used a pre post study design using a historical control.

Setting: The guidelines were trialled in two paediatric intensive care units at different hospitals in an Australian metropolitan city.

Participants: Patients admitted to the PICU and ventilated for ≥24 hours, aged more than one month of age and not admitted for seizure management or terminal care were recruited into the study.

Intervention: A trial of guidelines for sedation and analgesia management for critically ill children including algorithm and assessment tools.

Primary and secondary outcome measures: In addition to key outcome variables (ventilation time, medication dose and duration, length of stay), feasibility outcomes data (recruitment, data collection, safety) were evaluated. Guideline adherence was assessed through chart audit and staff were surveyed about merit and use of guidelines.

Results: The guidelines were trialled for a total of 12 months on 63 patients and variables compared to historical control group (n= 75). Analysis demonstrated significant differences in median Morphine infusion duration between groups (pretetst 3.63 days (87hrs) vs posttest 2.83 days (68hrs), *p=0.05*) and maximum doses (pretest 120mcg/kg/hr vs postest 97.5 mcg/kg/hr) with no significant difference in ventilation duration. Chart audit revealed varied use of tools, but staff were positive about the trial and the perceived impact the guidelines had on practice.

Conclusions: The sedation guidelines in this study appear to be feasible in practice, and impacted on the duration and dosage of agents without adversely impacting on ventilation duration or length of stay. The results of the study have laid foundation for follow on studies in withdrawal from sedation, point prevalence and longitudinal studies of sedation practices as well as drug trial work.

Strengths of study:

- Detailed outline of guideline development process based on consensus paper and available evidence
- Original dual site feasibility (pilot) study testing impact of guidelines on patient, quality and practice outcomes
- Generation of clinical and trial process data to inform future trial work

Limitations of study

- No firm evidence or 'cause and effect' can be concluded due to pre/post study design and small sample size

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Introduction

Sedation and analgesia are necessary components in the care of all critically ill patients, especially those requiring mechanical ventilation. The main indications for their use include: to reduce patient pain, anxiety and agitation, induce amnesia, facilitate mechanical ventilation, prevent the displacement of endotracheal tubes, and decrease cellular metabolism [1-3]. The detrimental impact of poor sedation practices in intensive care units has increasingly become a focus for researchers and clinicians and extends from concerns for both under sedation to over sedation[4]. Both under and over sedation has the potential to lead to agitated patients with compromised short term safety issues and impact on duration of ventilation and length of stay.[5 6]. The consequences of prolonged use of sedative and analgesic agents in the intensive care unit patient include central nervous system activation, gastrointestinal disturbances, and sympathetic hyperactivity. These signs and symptoms have been related to tolerance and withdrawal phenomena and also hold implications for the patient's physical and psychological well being as well as health care costs [7-9]. These risks are potentially amplified in the critically ill child in the paediatric intensive care unit (PICU) due to the developing brain[10 11]. **The aim of this study was to develop, implement and evaluate guidelines for sedation and analgesia management in the PICU as a part of program of research in this area and as a prelude to future trial work.**

Background

The 2006 consensus guidelines on sedation and analgesia in critically children established a standard for clinical practice in paediatric intensive care units (PICU) [12]. The guidelines' key recommendations include advice on a loading dose and administration for analgesia and sedation medication, the use of validated pain and sedation assessments tools, withdrawal assessment, and the inclusion of non-pharmacological interventions. Surveys of sedation and analgesia management in PICUs have identified a lack of specific protocols for sedation and analgesia management [13-15]. This research has also highlighted wide variations in physician practice, nursing assessment, pharmacological agents, as well as administrative

methods and doses. Limited use of assessment tools has also been reported, and there were no measurements or guidelines for withdrawal of drugs.

INSERT TABLE 1 Summary of 2006 consensus paper recommendations for sedation management of critically ill children.

A number of studies have attempted to evaluate the impact of sedation and analgesia guidelines in PICU, however the results have been varied [16-20]. Each of the studies successively added to our knowledge and understanding of sedation and analgesia management in critically ill children. However, differences in guideline specifics, models of care, and study design may contributed to the varied outcomes observed in the studies and limited their ability to inform best clinical practice. The aim of this study was to develop sedation and analgesia management guidelines based on the 2006 consensus recommendation and test their feasibility and acceptability in practice as a prelude to rigorous trial evaluation of guidelines in practice.

Methods

Aims and Objectives of Study

The main aim of this study was to develop, implement and evaluate locally developed guidelines for sedation and analgesia management on patient outcomes. Secondary aims were to evaluate the feasibility and acceptability of the guidelines in practice.

Study design

This dual site study used a pragmatic pre and post test design to examine the feasibility and impact of the guidelines on patient and practice outcomes. A chart audit was used to assess the implementation fidelity and a (nursing) staff survey was conducted to ascertain staff

perceptions of guideline utility and acceptability in practice. The study received full ethical and institutional approval (HREC/05/QRCH/19) The requirement for consent was waived.

Setting

The study units were two eight-bed, mixed medical surgical PICUs located at tertiary referral children's hospitals admitting patients from 0-16 years of age. Post registration qualifications in either paediatrics, ICU or PICU were held by approximately 48% of the nursing staff.

Sample and Participants

The target population was all patients ventilated for ≥ 24 hours within the PICU, aged more than one month of age and not admitted for seizure management or terminal care. All eligible patients were consecutively enrolled into the study. As the main aim of the study was feasibility rather than hypothesis testing, the statistical power of the sample was of reduced importance. Charts of patients in the post implementation phase were the focus of the audit. All nursing staff were invited to participate in the survey gauging staff perceptions and use of the guidelines in practice.

Guideline development

The sedation and analgesia guidelines for this study were developed around an algorithm for each of the identified phases of sedation (See Appendix 1). The key recommendations of the guidelines developed and tested in this study were based on the key recommendations in the 2006 consensus paper which was summarised in Table 1 [12].

Comment [SK1]: Guidelines are offered as an appendix to the article as they are 6 pages long. These can made feely available to all on line readers and upon request to the corresponding author for hard copy readers. This appears to the be the current manner journals deal with large appendices.

A range of non pharmacological strategies to minimise patient stress and pain, and optimise comfort are supported by varying levels of evidence ranging from case studies to Cochrane systematic reviews. These were not new strategies but it was important to incorporate them into the guidelines to promote a holistic approach to pain and sedation management and

reflect the recommendations of the consensus guidelines. Strategies recommended were aimed at moderating the PICU environment where possible (i.e. minimising high intensity light and noise, ensuring rest periods) [21 22]; minimising discomfort of invasive devices; regular repositioning and limb support with pillows, pressure relieving devises or swaddling [23 24]; monitoring and optimising hydration, nutrition and essential cares (e.g. oral and eye care); supporting parental visitation and reassurance as well as therapeutic (non-technical) touch [25 26].

New assessment scales for behavioural state, pain and withdrawal assessment were integral to the guidelines. These included the State Behaviour Scale (SBS)[27 28], the Multidisciplinary Assessment of Pain Scale (MAPS)[29-32] and the Opioid Benzodiazepine Withdrawal Assessment Scale (WAS) [33 34].

The three phases of sedation (acute, plateau and weaning) management were derived from patterns observed in a retrospective audit conducted earlier by the research team [35 36] and from the literature [9 12 37-39]. The guidelines reflect the dynamic nature of a PICU patient's admission and allow for movement between and within phases according to patient need, response and condition.

As the main aim of the guidelines was to improve consistency in medication practices, it was vital to get a consensus on prescribing practices within the study units. Even the authors of the consensus guidelines note that there is limited evidence to draw on and the recommendations were based on knowledge of drug pharmacokinetics, case study reports, expert opinion, and also the understandings of pain management, drug tolerance and withdrawal medicine. Morphine and Midazolam are the most common analgesic and sedative agents used in PICUs [3 14 40 41] and the drugs of choice in the study units. They are typically used in combination as together they have a synergistic effect that often allows for use of lower doses. Midazolam doses can be reduced as much as 30%-50% when combined

with an opioid [42]. Nonetheless, prolonged and/or heavy sedation persists in critical care units, and as a result tolerance and withdrawal syndrome complicate recovery.

In the Acute Phase the guidelines proposed a significant loading dose to achieve the desired analgesia and sedation goals, followed by regular patient assessment and incremental medication changes to achieve and maintain these goals. If the maximum dose allowed was reached (i.e. 300mcg/kg/hr for past 4 hours) then use of adjunct or alternative drugs was recommended (i.e. clonidine, fentanyl). “Drug cycling” has been reported to be helpful in the United Kingdom, where 25% of PICUs surveyed reported rotation of sedatives to minimize tolerance [3]. In another paper, consultant intensivists conducted biweekly chart reviews of each patient in the ICU and regularly change their sedation regimens [43]. Although these authors imply success with drug tolerance, no numerical data was offered in support.

Once in the Plateau phase, the key change in practice was the recommended conversion from intravenous to long acting enteral agents. This approach is based on the principles of narcotic withdrawal where withdrawal syndrome is managed by conversion to an orally active drug with a longer half life (such as methadone or diazepam) that has a more steady state serum concentration, more readily facilitating a slow taper of the drug and minimizing the severity of withdrawal symptoms or even development of withdrawal syndrome [44-47]. The advantages of methadone are an oral bioavailability of 75% to 80% allowing for oral administration, and a prolonged half-life of 12-24 hours, allowing twice daily administration (ibid). There is a general reluctance to use diazepam for critically ill patients because of its long elimination and concerns about excessive and prolonged sedation. However, similar to methadone, diazepam’s long acting active metabolites theoretically should result in small changes in serum drug concentrations and may decrease fluctuations in sedation state and therefore be a more appropriate agent for long term sedated patients [39].

The formal acknowledgement of a Sedation Weaning phase with a dedicated assessment tool and tapering regime was new practice for the study units. No validated opioid or benzodiazepine weaning schedule was found however a consensus of opinion across the literature supports daily reduction of 5% to 10% or an initial reduction of 20% to 40% and followed by a 10% reduction once or twice daily, depending on patient response [39 48]. The protocol for sedation weaning incorporated into these guidelines approximated these recommendations.

Guideline Implementation

The guidelines encompassed many changes in practice: new assessment scales, standardising of practice, conversion to oral agents, algorithms, and a discreet weaning pathway. In the interest of maximising staff understanding and uptake of the tools, a phased implementation process was adopted with the gradual introduction of each tool into the units, followed by orientation and implementation to the algorithm phases and medication administration. Staff in-services introducing the study and guidelines were held over an initial fortnight with phased introduction and implementation of each assessment tool over the following months. These were further supported by bedside education on tool use and supplemented by information and teaching aids on the units' computer system.

In practice, the PICU team set sedation and analgesia goals as part of the daily patient review and staff at the bedside (usually nurses) used the guidelines to achieve the set goals.

Outcome variables

Data was collected from all eligible patients over 24 months (12 months historical control and 12 months post implementation), plus of a break for the implementation period. In addition to the main study outcomes, the pilot study collected outcomes to establish feasibility of the protocol and processes. Feasibility data outcomes included the success of screening and recruitment strategies; tested data collection and entry processes; confirm required costs for Research Nurse time, and produce further estimates of ventilation times and medication

dosing, that can be used to finalise sample size requirements for the larger trial, and inform funding applications for same. The main study outcomes measured included total ventilation time (TVT), sedation doses and duration, length of stay in the PICU (LOS), plus quality indicators such as, accidental extubation and readmission rates. Potentially confounding variables collected included patient age, gender, diagnosis, and the Paediatric Index of Mortality (PIM2) as a measure of acuity. Nurses in the study setting routinely collect and record standard demographic and biophysiologic patient measurements on the local computerised information system. The revised paediatric index of mortality (PIM2) is a simple model of mortality in paediatric intensive care based on admission data and uses ten explanatory variables [49]. Guideline fidelity was measured through chart review using an audit tool based the 19 key components of the guidelines. Staff perceptions were ascertained through administration of a researcher developed survey with questions on ease of use, impact on practice, perceived benefit, facilitation of team management, and promotion of nurse autonomy at bedside. Staff members were also given the opportunity to comment on strengths and limitations of the guidelines.

Statistical Analysis

Data were analysed using PASW 18.0 (SPSS Inc.). Descriptive statistics were used for demographic data. Continuous values reported were medians and ranges due to the large spread of the data. Categorical variables were reported as counts and percentages. Non parametric Mann Whitney or Cross tabulation and Pearson's Chi Square were performed to compare groups. The probability of remaining ventilated between groups was analysed using survival analysis. Adherence to guidelines was reported in counts and percentages. The influence of diagnostic group on guideline adherence was analysed using Pearson's Correlation and comparison of means using student's T-test. Survey responses were reported in counts and percentages as well as significant themes derived from qualitative data.

Results

During the two study periods (12 months each) 173 and 235 patients were ventilated in the respective pre and post guideline implementation periods. After screening for eligibility 75 and 70 patients were enrolled into the pre and post groups. Seven patients were lost to the study in the posttest group because of deviation from research protocol,,, one group of parents did not consent to use of the drugs, and transfer to another hospital. Ultimately there were 75 in the control group and 63 in the post implementation group. Data were analysed on a *per protocol* basis. Figure 1 demonstrates the sampling framework and exclusion criteria.

INSERT FIGURE 1

Table 2 shows the main characteristics measured for each sample. Both groups were comparable with no significant differences between age, weight, sex, or reason for admission. There were also no significant differences identified between the TVT and LOS for each group. There were no incidents of accidental extubation or readmission within 48 hours for subjects in either group for the study.

Table 3 shows the different drug characteristics between groups, demonstrating a greater variance in drug usage. The decrease of 19 hours in the median infusion time of Morphine between groups approached significance (87hrs vs 68 hrs, *p=0.059*). There were changes in the median minimum and maximum Morphine doses, though not significantly. A reduction of 11 hours was identified with median infusion of Midazolam between groups, however this difference was not significant. Significant changes in the median minimum and maximum doses of Midazolam were observed (MIN 10mcg/kg/hr vs 17 mcg/kg/hr, *p <0.001* and MAX 120mcg/kg/hr vs 180mcg/kg/hr, *p<0.001*).

INSERT TABLES 2 & 3

Applying the Kaplan-Meier curve of risk to the probability of remaining ventilated to each group demonstrated that posttest group did not have an increased risk of remaining ventilated (see Figure 2). The probability of remaining ventilated was reduced in the posttest group (by just less than a day at 21 hours); however this was not statistically significant.

INSERT FIGURE 2

Other significant changes in practice were the greater use of adjunctive and alternative medication, in particular methadone. Results showed that prior to the guideline implementation there was limited use of alternative medications (1-2 alternative medications or even none). Post guideline implementation the numbers of alternative medications used increased. More detailed analysis revealed a significant difference with the use of Methadone pre 3% - post 33% *p<0.001;* Diazepam pre 5% - post 25%, *p=0.001;* Chloral Hydrate pre 32% - post 58% *p=0.002;* Propofol pre 60% - Post 20% *p<0.001;* and Neuromuscular blockade agents pre 60% - post 47.6% *NS.*

Implementation fidelity (Chart Audit)

Sixty-three charts from the post implementation period were reviewed to identify if staff had followed at least 75% of the 19 key components of the guidelines and quantify the level of assessment and scoring. Overall adoption was achieved in 23 (36%) of the charts audited. Separate analysis within each of the phases demonstrated that adoption was achieved in 30 (47.6%) in the acute phase, 23 (36.5%) in plateau, and 25 (39.7%) in the weaning phase. Pain and sedation scores were assessed and documented in 95% (n=60) of charts in the acute and plateau phases, and 85% (n=54) of charts in the weaning phase. The withdrawal score was assessed and documented appropriately in 75% (n=47) of charts.

Staff survey

The response rate was 49% (n=54). Participants' responses were divided into four categories: awareness/use, strengths, limitations and suggestions for improvement. Fifty-two (96%) staff regularly referred to the guideline to assist with decision making and to provide prompts and cues. There appeared to be some confusion as to who was primarily responsible for the initiation of the guidelines, with 12(23%) suggesting is was the consultants' responsibility and 32(60%) stating it was the bedside nurse. Table 4 outlines further responses.

INSERT TABLE 4

Perceived strengths of the tool included the structured nature of the guidelines, promotion of consistency in practice and the resulting increased awareness regarding sedation management. Conversely perceived limitations included the perceived complexity of algorithm, confusion with delineation and movement between phases, and the lack of accommodation of increased drug tolerance with long term patients. Staff suggested simplifying the algorithm and using larger print, incorporating recommendations for short term patients and providing clinical example as guides. . Table 5 provides the staff comments on perceived strengths and weaknesses of the guidelines Overall four major themes were expressed by study participants (see table 5): (1) a knowledge deficit about some aspects of the guidelines, (2) high value placed on individualised patient care, (3) perceived ineffectiveness of the guidelines for some patients, and (4) disagreement between doctors and nurses on responsibilities.

INSERT TABLE 5

Discussion

This pragmatic study demonstrated that the guidelines were feasible and acceptable in practice. The use of guideline directed sedation and analgesia management allowed the

PICU team to achieve the patient's sedation goals quicker without significantly increasing ventilation times or PICU length of stay. Full adoption of all aspects of guidelines was not realised but results demonstrated improved levels of patient assessment, increased use of enteral agents, and largely positive feedback on guidelines in practice.

The observed increases in median minimum and maximum doses of Morphine and Midazolam do not seem to have increased patient TVT or LOS, and in fact the duration of each infusion was reduced, significantly in the case of Morphine. Similar changes in medication administration were observed in other PICU guideline studies [16-20].

The results of Kaplan-Meier Risk analysis demonstrate that there was reduced risk of remaining ventilated in the post-test group though this was not statistically significant. However, a median difference of 21 hours between groups may be viewed as 'clinically significant' as this time difference in the clinical setting could translate to earlier extubation and/or discharge. A reduction in ventilator duration was also observed in two other studies. Larger, randomised trial studies are warranted to further explore this important outcome.

The results also revealed the huge spread of the clinical data and the challenge this posed for researchers. Follow on studies would possibly need to consider subcategories of patients i.e. short, medium and long term ventilated and analysing within these categories.

The guidelines and implementation process in this study also appear to have significantly increased awareness and usage of alternative medications to complement or replace the Morphine/Midazolam. This was particularly evident with the use of Methadone and Diazepam. Use of Methadone rose from 3% pre test to 33% post test. Use of Diazepam rose for 5% pre test to 25% post test. One of the key recommendations to emerge from the literature and therefore included in the guidelines was the transition from continuous intravenous analgesia and sedation to regular oral agents. Prolonged administration of

opioids and benzodiazpines may result in the development of drug tolerance and then withdrawal syndrome if these agents are abruptly discontinued [9 38 50 51]. Research has shown that this can be prevented by slowly tapering the intravenous administration of the drug or switching from intravenous morphine and midazolam to orally active drugs with a longer half-life, such as methadone and diazepam [45 47]. In general the increased use of adjunct medication demonstrated the heightened awareness of the appropriate use of complimentary drugs to help the patient reach the required sedation goal in a timely manner.

Sedation, Pain and Withdrawal scores were all captured but difficult to summarize meaningfully as a research variable. We recommended that a useful variable for follow in studies be to calculate the percentage of time each patient spent in a designated 'zone' and determining appropriateness and success /failure of management accordingly.

The audit of implementation fidelity demonstrated that the assessment and documentation of patient's pain and sedation was well recorded, reflecting sound staff understanding and uptake of the new assessment tools. The adoption score for the withdrawal phase was the lowest of the three phases, which may have resulted from less familiarity and knowledge with the tool and phase. This is consistent with findings were found in a review of similar studies [52]. Suggested reasons for non-adherence included complexity of guideline or algorithm, staff not valuing or understanding goal of guideline, perceived redundancy of guideline if staff already competent practitioners in this area (ibid). Potential solutions to these issue included ongoing staff education and timely feedback related to the guideline to continuously reinforce importance, ease of use, and troubleshoot issues[53]. In addition to surveying staff opinion, it is also important to conduct periodic chart audits to quantify guideline fidelity. This will help minimise self-report bias as was somewhat reflected in this study[54]. Staff perceptions of guideline principles and use were positive although level of adherence variable. So the full impact of the guidelines were not realised.

In conjunction with the audit, a survey of staff perceptions and attitudes were undertaken to establish if these influenced adoption of the guidelines. In line with other similar studies, staff were largely positive and constructive in their feedback[18 55 56]. All feedback has been utilised to improve the guidelines. Engaging staff and providing feedback during the process of procedural change is a vital step in optimising translation to practice.

The importance of the findings of this study are that they demonstrate that collaborative guidelines for sedation management can optimise the PICU patient's sedation and analgesia management without compromising quality of care (TVT, LOS, quality indicators). The results are similar to those in the adult population where guideline or protocol driven sedation has been linked to a reduction in duration of continuous intravenous sedation, ventilation time and associated health care costs [57-61]. Evaluation of feasibility outcomes has aided in development a realistic plan about participant recruitment, staff education to optimise guideline fidelity, safety of guidelines in clinical practice and collection of key outcome variables.

Implications & Recommendations

No definitive causal effect can be attributed to the guidelines on outcomes due to the pre post study design and small sample size. Conducting the study in two units assists with the generalisability of the study and its results. Some specifics of the guidelines and algorithm, however, might need modification to reflect local practice. For example, use of different drugs (fentanyl instead of morphine) and different patient populations (post cardiothoracic surgery). The study results are most useful in informing the structure and outcome measures for a follow on clinical trial in this area.

Results from the study, audit and survey have informed changes and modifications to optimise staff understanding and use of sedation guidelines in practice. Weaning from sedation agents and the concept of withdrawal appear to be areas of practice that need more

attention. The researchers went on to trial and evaluate a revised withdrawal assessment tool and a study comparing the outcomes of Dexmedetomidine versus Midazolam is about to commence. The study units plan to continue to use the guidelines and tools in their modified form pending the results of larger trial work recently completed in the USA. The modern ICU is an important focus for quality improvement efforts. Guidelines cannot automatically guarantee improved quality of care; however, they do direct the clinician in the pursuit of this objective particularly when supported by high level evidence.

Contributorship statement:

All three authors, Samantha Keogh, Debbie Long and Desley Horn meet the key three ICMJE guidelines for authorship with each having made (a) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content; and (c) final approval of the version to be published.

Competing interests

None of the authors have any competing interest or financial disclosure related to this study to declare.

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Data sharing statement

A copy of the guidelines can made available by emailing Debbie.Long2@health.qld.gov.au.

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Samantha Keogh RN PhD
Senior Research Fellow | Griffith University
NH&MRC Centre for Research Excellence in Nursing
Honorary Research Fellow | Royal Brisbane & Women's Hospitals
c/- Research Centre for Clinical and Community Practice Innovation
Griffith University, Nathan Campus, Health Science Building (N48)
170 Kessels Road, Brisbane Qld Australia 4111

21 October 2014

Dear Editor

Thank you to you and the reviewers for your constructive criticism of the submitted manuscript. I have attached a detailed response to the reviewers' comments as well a revised version of the manuscript with tracked changes.

This study was part of an established program in the area of sedation and analgesia management on the unit that had already included a Retrospective study on patterns of sedation and pain management practice (presented at National Meeting and served as historical control) as well as a Survey on sedation and analgesia practice across PICUs nationally (published in peer reviewed Critical Care Journal). The researchers went on to trial and evaluate a revised withdrawal assessment tool and a study comparing the outcomes of Dexmedetomidine versus Midazolam is about to commence. The study units plan to continue to use the guidelines and tools in their modified form pending the results of larger trial work recently completed in the USA.

The development and reporting of this study was challenging. We have put significant detail about Guideline development including guiding references in the manuscript to inform readers about rationale and available evidence guiding each recommendation. The concept of two papers outlining 1. Guideline development and, 2. Short report on evaluation - was in fact rejected by previous journals! So we attempted to be as succinct yet complete describing the whole process as it occurred at the time. In essence, a truly pragmatic clinical study 'pilot testing' locally developed guidelines developed. To reduce the words we have removed the detailed summary of other guideline studies and merely referenced them for the readers' information.

A lot of effort went in to developing and conducting this study as well as writing it up. We realize its limitations and have reported these but sill feel it has value in revealing lessons learnt from the process and knowledge gained.

We hope that you are able to consider publication of the revised manuscript.

Yours faithfully

Samantha Keogh
(corresponding author)

Responses to BMJ (Open Access) Reviewer(s)' Comments to Author:

Editorial comments
1. This isn't a trial in the sense of being an RCT. The title and the abstract could be clearer about the study design
OK Title adjusted

2. the abstract should be clearer about what the control group was; the language of RCTs has crept in but this wasn't one
OK pre post study using a historical control

3. Please include information in the conclusions (and briefly in the abstract) about how this work has informed future work
This study was part of an established program in the area of sedation and analgesia management on the unit that had already included a Retrospective study on patterns of sedation and pain management practice (presented at National Meeting and served as historical control) as well as a Survey on sedation and analgesia practice across PICUs nationally (published in peer reviewed Critical Care Journal). The researchers went on to trial and evaluate a revised withdrawal assessment tool and a study comparing the outcomes of Dexmedetomidine versus Midazolam is about to commence. The study units plan to continue to use the guidelines and tools in their modified form pending the results of larger trial work recently completed in the USA.

Reviewer Name Lyvonne Tume RN PhD
Institution and Country Alder Hey Children's NHS FT, UK
Please state any competing interests or state 'None declared': None declared

Dear Authors,
Thank you for your interesting and relevant paper. I have a few queries and some suggestions to improve the manuscript. I think the manuscript is quite long and wordy and could be made more succinct and reduced to around 3500 words without losing the content.
In the abstract it should be made clear the design is a before and after study.
Ok Review of litereature reviewed in background significantly reduced allowing manuscript to focus of guideline development and evaluation process.
Research design explicitly stated in abstract

Initially I was quite confused about the number of patients included in a 12 month period, then it became clear that you have undertaken a power calculation which predicted 75 per group, which would have been helpful to know earlier on.
Statement about sample was in 'participants' section of study. Subsequent advice (from both fellow reviewer and other researchers in area) the nominal power calculation was removed given focus of study not about testing hypothesis and more about evaluating absolute impact, feasibility in practice and acceptability by staff.

I am very surprised that given a reduction in ventilation time by 21 hours (nearly a whole day) this was not statistically significant, it is certainly clinically significant and i think this should be highlighted. However if there are not people competent in extubation around when the child is 'ready' to be extubated or the nurses in your unit cannot do this, then this will influence ventilation duration and should be mentioned somewhere or included in a limitations section.
Given small and likely underpowered sample size it is not surprising difference in ventilation was not statistically significant. However potential for clinical significance has been enhanced as suggested. Though I am careful not to overstate findings give limitations of study.

Other points, throughout the paper i think you should replace 'patient' with 'child'.
OK changed

On P.4 line 17 you claim both under and over sedation cause agitation, well i think the main issue with over sedation is increased ventilation time, along with more dependence, tolerance and possibly withdrawal.
Yes we agree so have included in in paragraph though some already present.

The introduction should be a short succinct paragraph with the aim clearly stated and your separate background section could be shortened substantially, you can refer to those studies in the discussion, where there should be more reference to the literature.
Ok will rewrite and precis

On p8 line 11 you state there are no normative values for ventilation time, there may not be normative values but certainly in the UK, the large audit database (PICANET) shows that across 31 PICUs the median ventilation time is 3 days - this would not be dissimilar to Australia I would imagine. This data is freely available online.
Yes, thank you we also have normative national values from National reports but as mentioned previously power calculation statement now removed from manuscript.

There are a lot of tables and graphs, but not one of your actual guidelines, this would have been useful, because I am not clear even how often sedation, pain etc were scored.
Guidelines were uploaded as supplemental material on submission of manuscript and are usually offered as an appendix (as 6 pages long) to online viewers or via communication with corresponding author. You should be able to access them also. This is what was recommended in guidelines.
Description and rationale for each phase was described in Guideline Development section

On p.10 and 11 you refer to 'weaning' please specify this as 'sedation weaning' as it could be confused with ventilation weaning and the 2 things are inextricably linked.
OK text added

On p 12 line 48, you say 'some patients'....please specify how many.
OK –number added in to test actual number was in Figure 2.

On p. 14 line 21 'chart audit' might be better worded as @implementation Fidelity'.
Ok added

On p. 14 line 42 you mention the survey but in the methods there is no mention (I could see) of how the survey was developed, types of questions, piloted etc and who it was given to? was it just nurses or medical staff too?
Survey was referred to in design statement and added to sample statement. Additional detail was already located in outcome variables as follows:

"Staff perceptions were ascertained through administration of a researcher developed survey with questions on ease of use, impact on practice, perceived benefit, facilitation of team management, and promotion of nurse autonomy at bedside. Staff members were also given the opportunity to comment on strengths and limitations of the guidelines. "

The discussion could be shortened and refer to more literature rather than just restating results (p. 16 line 19-23).
Soe reference to other PICU guidelines studies added. A number of other references helping to confirm or clarify results already present (e.g. medication withdrawal, guideline fidelity, staff feedback).

Finally I am not sure what table 4 really adds to the paper.
It would be useful and would strenghten the paper to address these issues.
Table 4 details responses to Staff survey

Reviewer Name Yoanna Skrobik
Institution and Country Université de Montréal
Canada
Please state any competing interests or state 'None declared': none declared

This pragmatic pre-post implementation study's stated aim is the development, implementation and trial of locally developed guidelines for sedation and analgesia management in pediatric ICU patients. The authors audited charts and surveyed caregivers (nurses) for ease of use of the new guidelines. The tools described to assess the patients were the State Behaviour Scale, the Multidisciplinary Assessment of Pain Scale (MAPS) and the Opioid Benzodiazepine Withdrawal Assessment Scale (WAS). A broad variety of pharmacological interventions (varying drugs with varying half-lives in patients with very different lengths of stay) are described. A small sample of pre-implementation patients (75 patients in the pre and 63 patients in the post group) were evaluated. Study outcomes were total ventilation time (TVT), sedation doses and duration, length of stay in the PICU (LOS), and accidental extubation and readmission rates. Overall, opiate use and duration were reduced, and other outcomes were not different. The protocol was found to be

feasible and acceptable to the majority of respondents (49% of the caregivers).

The study is interesting and important as individualized symptom management for pain and sedation is becoming recognized as an important outcome determinant in the critically ill.
The description of the protocol merits clarification. The psychometric validation of the scales applied to this pediatric population is not described, nor is caregiver evaluation performance for the individual scales.
This was not the purpose of the study. The development and validity of the respective tools was conducted by the authors respectively who are duly referenced. These are now widely used in the PICU community except for the WAS tool which is known better known in revised form WAT-1. Given already lengthy state of manuscript we didn't feel paper had room or scope for this.

It is also not clear on whether pain and sedation levels were differentiated or prioritized (i.e. with an attempt to evaluate pain first and sedation level second), or whether targeted analgesia levels or sedation levels were any different between the pre and post groups.
Yes, recommendation for individual patient goals determined daily as mentioned in Guideline implementation section and detailed in Guidelines, which were uploaded as supplementary material to be offered as Appendix (as is 6 page document).

Finally, the variety of pharmacological interventions and the varying pharmacokinetic characteristics of the administered drugs (particularly those infused over longer periods in the patients who had very long (30-75 days) periods of mechanical ventilation or long lengths of stay) confound the interpretation of the role the protocol played in the differences between the pre and post group. Providing the 'target range' data might better answer this question.
Yes we don't disagree with the potentially confounding influences of such a heterogeneous population; hence the 'pilot nature' of this study and the study results being considered most useful in informing the structure and outcome measures for a follow on clinical trial in this area.

Reviewer Name Saskia N. de Wildt
Institution and Country Pediatric intensivist, clinical pharmacologist
Erasmus MC - Sophia Children's Hospital
Rotterdam, The Netherlands
Please state any competing interests or state 'None declared': None declared.

Implementation of sedation protocol may improve patient outcome. The authors present the outcome of such an implementation in 2 PICUs.

Major comments:
The authors are not clear about the objectives of the study. The primary objective mentioned is 'to develop sedation and analgesia management

guidelines and test their feasibility and acceptability in practice', however, in the abstract and the results they mention patient outcome data as primary result, despite small sample size. Please clarify.
Aim and objective statements through document made uniform for clarity and results reported accordingly to reflect this.

Overall, it took me a long time to grasp what the authors did and how they did it.

The overall lack of detail on the sedation protocol and the other guidelines (the table is not very detailed), as well as the missing information on how exactly adherence was measured, make this paper hard to understand and the conclusions not very useful for extrapolation. did every patient have score list?

Maybe they want to put too much in one manuscript.
I would suggest a manuscript describing how they came to the protocol and how it was implemented (where nurses trained to do validated pains scores?) and another paper on the effect of implementation.

In answer to both above statements, herein lay the challenge of reporting and writing up this study. In fact we have put significant detail about Guideline development including guiding references. The concept of two papers outlining 1. Guideline development and, 2. Short report on evaluation - was in fact rejected by previous journals! So we attempted to be as succinct yet complete describing the whole process as it occurred at the time. In essence, a truly pragmatic clinical study 'pilot testing' locally developed guidelines developed. To reduce the words I have removed the detailed summary of other guideline studies and merely referenced them.

There is no information on the sedation management protocol used in this study. Instead, a summary of the consensus guidelines is added in table 1. Is this how they are used in the unit, or is there an extended version, consider uploading this a supplementary file. I suggest to add the sedation protocol (flowchart?).
Guidelines were uploaded as supplemental material on submission of manuscript and are usually offered as an appendix (as 6 pages long) to online viewers or via communication with corresponding author. You should be able to access them also. This is what was recommended in guidelines.
Description and rationale for each phase was described in Guideline Development section.

The summary of consensus paper guiding the development of detail of the study guidelines has been brought forward to distinguish it from the body of the study.

The introduction and methods section can be significantly shortened. There is no need to discuss all studies in detail in the introduction. In the methods section, the authors discuss the consensus guidelines and 'drug cycling'. This is not appropriate in this section.

The rationale for the steps and phases of the guidelines form an essential part of the guideline implementation description.

In the discussion section the authors state that sedation goals were achieved quicker. However, this study shows no support of this statement. There are no scores of adequate sedation or sedation time. Please clarify. Ok. Acknowledged and removed. Sedation, Pain and Withdrawal scores were all captured but difficult to summarize meaningfully as a research variable. We recommended that a useful variable for follow in studies be to calculate the percentage of time each patient spent in a designated 'zone' and determining appropriateness and success /failure fo management accordingly. This has been added to discussion.

Minor comments:
- Sample size calculation: it is not clear how the authors have calculated the sample size. What was the total ventilation time of the retrospective analysis? ? remove
Given small and likely underpowered sample size it is not surprising difference in ventilation was not statistically significant. However potential for clinical significance has been enhanced as suggested. Though I am careful not to overstate findings give limitations of study.

- Setting: is the study performed on a medical, surgical or mixed PICU (instead of 'a range of diagnosis').
Setting description changed

- Study period: what was the study period? In the methods section the authors mention a study period of 6 months pre- and 6 months post-implementation, however, in the results they mention two study periods of 12 months each.
Typo corrected to 12 month each period

- Figure 1: please mention the reasons for exclusion.
Exclusion criteria in figure and also discussed in text

- Table 2 and 3: please mention median and IQR instead of range. Changed

additional comments:
Abstract: please specify which group the outcomes relate to (morphine dose and duration) Added

Page 6 line 17: the fentanyl units seem wrong (doses around 500 mcg/kg/h?)
Thanks you checked but then removed as this section précised considerably

Page 12 line 50: what is meant with 'deviation from study protocol or guidelines'? what is the difference between study protocol and guidelines? isn't this an outcome variable? Does this not present bias to the results?
Yes deviation from guidelines was an outcome variable as part of fidelity testing. It presents some bias in that only per protocol analysis was conducted, but as this was largely conducted as 'pilot study' and feasibility study no causal effect is claimed or reported.

It is not clear from the methods section that parents were asked for informed consent. Asking informed consent is a bit unusual when a new treatment algorithm is introduced in practice.
Ethics approval statement with reference made. No consent was not required for this study as met conditions for low and/or neglible risk. Statement added to manuscript for clarity.

Page 13 2nd paragraph: the description of results is ambigue: 'a reduction … between groups'> I assume a reduction from pre to post implementation? This should be worded more clearly. 10 mcg/kg/h midazolam seems very low. Are this medians for single patients? Or is this the median of the lowest dose (e.g. at weaning) for each patient. It is insufficient to only provide median/means and p-values, also the variability e.g. SD, IQR or range for each variable should be presented.
Description of what each variable is i.e. median minimum or median maximum are detailed prior to reporting of actual values. IQRs added

What is difference in protocol directed vs intervention group? Is this the same? Please use consistent wording throughout manuscript.
Sorry. Inconsistencies with language corrected.

It appears that a lot of effort has been put into developing these guidelines, implementing them and studying the effect, which are worth to be shared with the PICU community.
Thank you. Yes a lot of effort went in to developing and conducting this study as well as writing it up. We realize its limitations and have reported these but sill feel it has value in revealing lessons learnt from the process and knowledge gained.

As also noted above, the paper lacks in detail on methods and it should be strongly suggested to write two papers. As mentioned previously mentioned, Editors not receptive to this suggestion.

Consider adding experts on sedation research and on implementation to your team.
This study was part of an established program in the area of sedation and analgesia management on the unit that had already included a Retrospective study on patterns of sedation and pain management practice (presented at National Meeting and served as historical control) as well as a Survey on sedation and analgesia practice across PICUs nationally (published in peer reviewed Critical Care Journal). The researchers went on to trial and evaluate a revised withdrawal assessment tool and a study comparing the outcomes of Dexmedetomidine versus Midazolam is about to commence. The study units plan to continue to use the guidelines and tools in their modified form pending the results of larger trial work recently completed in the USA.

Figure 1: Sample framework

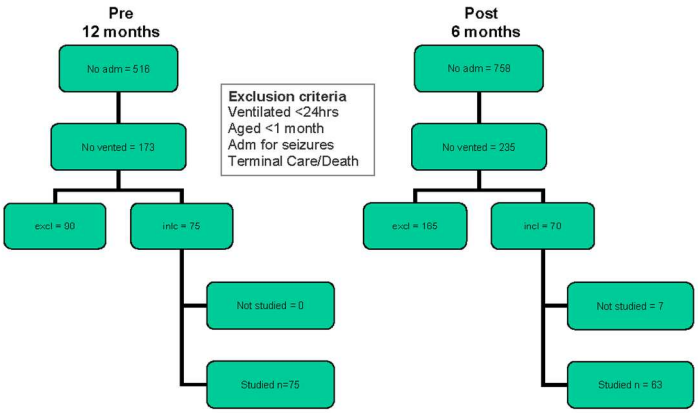

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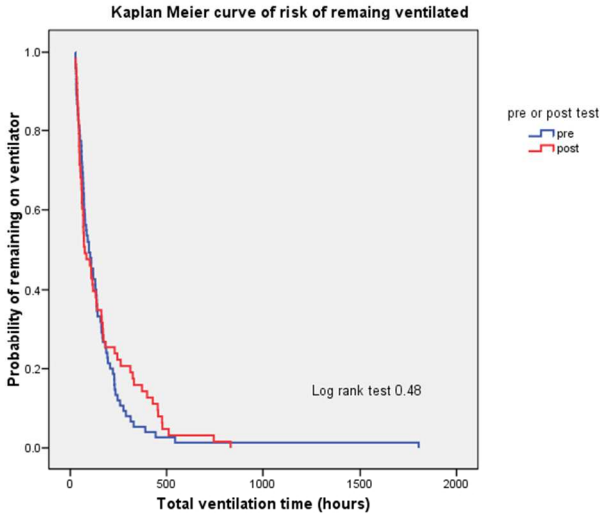
Figure 2: Kaplan-Meier Curve of risk of remaining ventilated between groups



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GUIDELINES FOR THE ADMINISTRATION OF SEDATION AND ANALGESIA IN MECHANICALLY VENTILATED CHILDREN

PURPOSE:
To outline the management of sedation and analgesia in critically ill children receiving mechanical ventilation.

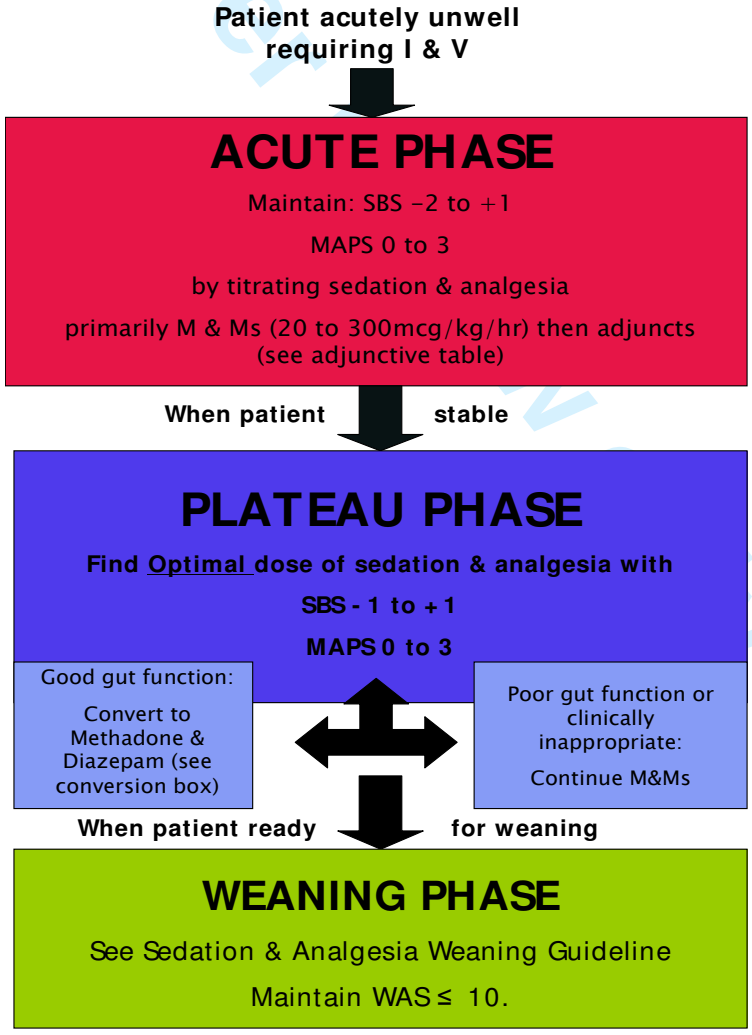
BACKGROUND / SUPPORTIVE DATA:
Sedation and analgesia are necessary components of the care of all critically ill children, especially those requiring mechanical ventilation. The main indications for the use of sedation and analgesia include: to reduce pain and discomfort, to reduce anxiety and agitation, to induce amnesia, to facilitate mechanical ventilation, to prevent the displacement of endotracheal tubes, and to decrease cellular metabolism. The consequences of prolonged use of sedative and analgesic agents in the PICU patient include central nervous system activation, gastrointestinal disturbances, and sympathetic hyperactivity. These signs and symptoms have been related to tolerance and withdrawal phenomena and hold implications for the patient's physical and psychological well being as well as health care costs.

Tolerance is one of the major reported adverse effects associated with continuous benzodiazepine infusions. Tolerance may be defined as a decrease in the effectiveness of a drug after prolonged use or as the requirement of larger doses to achieve the same effect. This phenomenon is due to an adaptation of neuronal cells and not a change of metabolism of the drug. One method of addressing this adverse effect, drug tolerance, is to recognise its occurrence and introduce alternative sedation agents titrated to an accepted sedation level.

A second adverse effect of the prolonged use of analgesic and sedation agents is withdrawal or abstinence syndrome. In paediatric patients, withdrawal syndrome is due to the development of tolerance to sedation and analgesic drugs not dependence or addiction. Studies have shown a strong positive correlation between large total doses of midazolam and the occurrence of withdrawal symptoms. Local, national and international audits have all shown that drug tapering is conducted in very few patients and that most patients have their sedation and analgesic agents abruptly discontinued. Thus, the incidence of withdrawal symptoms may be related to the infrequent tapering of sedation and analgesic agents.

There exists a plethora of literature discussing the adverse effects of sedation and analgesia in the critical care environment, particularly its prolonged use. There appears to be a consensus about the need and benefits of a systematic and coordinated approach to sedation administration, tapering and titration in the PICU.

SUMMARY OF SEDATION ALGORITHM:



EVIDENTIARY TABLE:

Strategy	Evidence
Use of protocol	The use of protocol directed sedation can reduce the duration of mechanical ventilation, ICU and hospital stay and can result in safe, cost-effective improvements.[1-5]
SBS – Sedation Scale	Reliable and valid scale for use in paediatric critical care.[6-8]
PICU MAPS – Pain Scale	Reliable and valid scale for use in paediatric critical care, particularly pre-verbal children.[9-12]
Withdrawal Assessment Scale	Combination of validated tool and Great Ormond Street Hospital protocol[13-18]
Accumulative dose	Up to 300 mcg/kg/hr for Midazolam
Weaning timeframes	[13, 19]
Mandatory review	[20]
Conversion to oral drugs	Diazepam, Methadone [24-26]

SUGGESTED PHARMACOLOGICAL TREATMENT OF PROCEDURAL PAIN AND DISCOMFORT:

Drug Group	Drug	Indications	Evidence
Topical Local Anaesthetic	Angel Cream EMLA	PIV/IAL insertion Venepuncture Arterial Stab Portacath access Lumbar puncture* CVL/ICC insertion*	[1-5]
	Lignocaine 2% & Chlorhexidine 0.05%	IDC insertion	[6, 7]
	Lignocaine 4%	Bronchoscopy*	[8, 9]
Sub-cutaneous injection	Lignocaine 1%	ICC/CVL insertion*	[2]
Disassociative Agent	Ketamine	CVL/ICC insertion Gastroenterology procedure Bronchoscopy Bone marrow aspiration Wound management procedure	[10, 11]
Short acting anaesthetic agent	Propofol	CVL/ICC insertion Gastroenterology procedure Bronchoscopy Bone marrow aspiration	[10, 12]
Short acting sedative & analgesic agent	Morphine & Midazolam	ETT Suctioning Movement/Position change	[30]

* used in conjunction with other drugs

SUGGESTED NON-PHARMACOLOGICAL MEASURES FOR OPTIMISING PATIENT COMFORT

Treatment	Evidence
Positioning & body support	[13-16]
Reassurance by staff and/or parents	[14]
Minimise discomfort of invasive devices (e.g. ETT, CVLs, and drainage tubes).	[14]
Optimise hydration, nutrition, essential cares (e.g. mouth, eye).	[17-19]
Massage, or rocking	[20, 21]
Swaddling	[22-24]
Non-nutritive sucking	[25-27]
Decrease external stimuli (noise, light, movement or handling)	[15, 28, 29]
Music therapy	[20]

SUGGESTED ADJUNCTIVE PHARMACOLOGICAL THERAPIES FOR MAXIMISING PATIENT COMFORT

Drug	Approach	Evidence
Propofol	2.5-3.5mg/kg stat then 7.5-15mg/kg/hr[30] ; 4-6mg/kg/hr[31]	[30-34]
Morphine	20mcg/kg prn	[30]
Midazolam	20mcg/kg prn	[30]
Ketamine	1mg/kg/hr	[30, 32, 33, 35]
Chloral Hydrate	25mg/kg q6h[36] maximum 5g	[35, 36]
Fentanyl	If allergic or renal failure 5-10mcg/kg/hrl	[30, 34, 35]
Promethazine	Oral 0.5mg/kg q6h Maximum 1mg/kg	[37]
Chlorpromazine	0.25-1mg/kg/q6-8h	
Clonidine	3-5mcg/kg q8h	[30, 35, 36, 38]
Haloperidol	0.1mg/kg- 0.1mg/kg q12h	[39]
Phenobarb	5mg/kg/day	[36]
Paracetamol	90mg/kg/24hrs- accumulation in hepatotoxic in pts with impaired LF-	[30]
Codeine	Max 1mg/kg/dose	[30]
Ibuprofen	10mg/kg q6h Precautions- asthma, renal impairment, under 6mths	[30]

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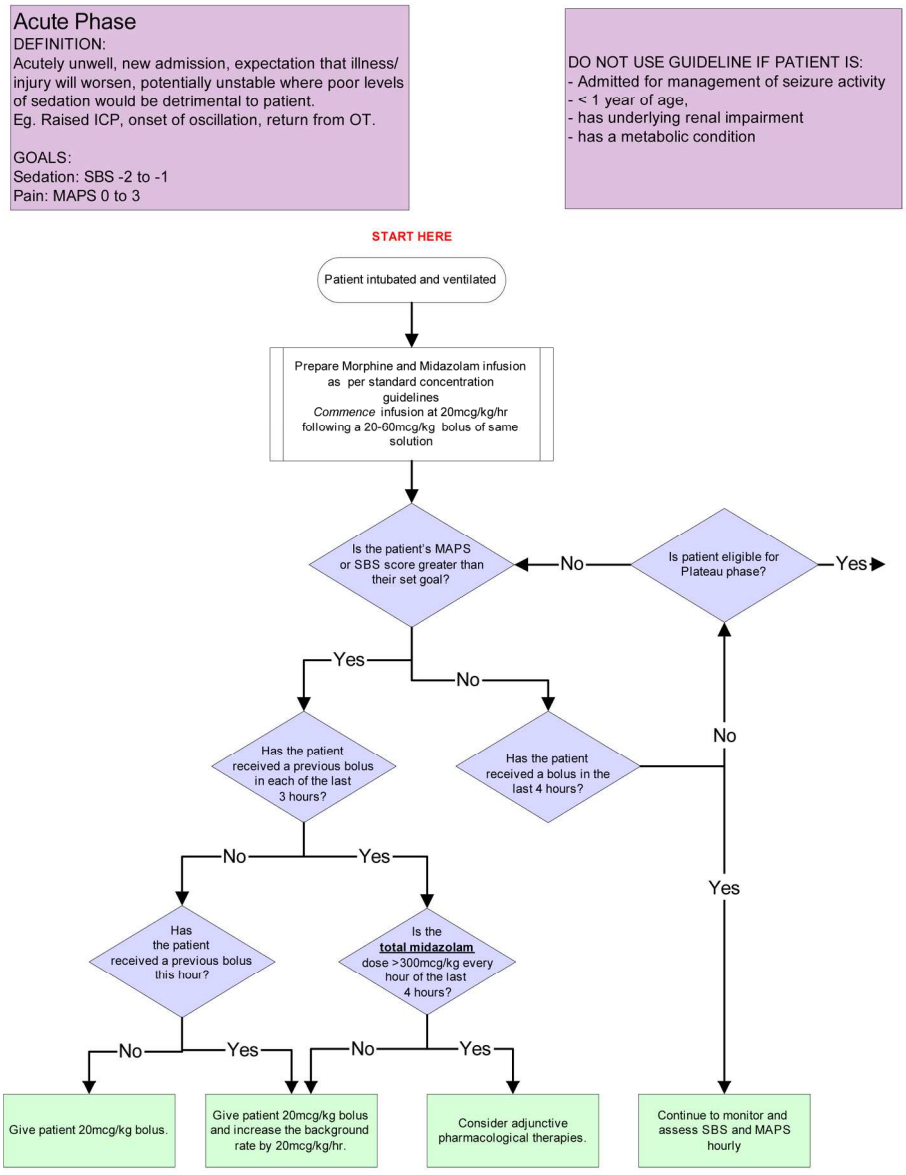

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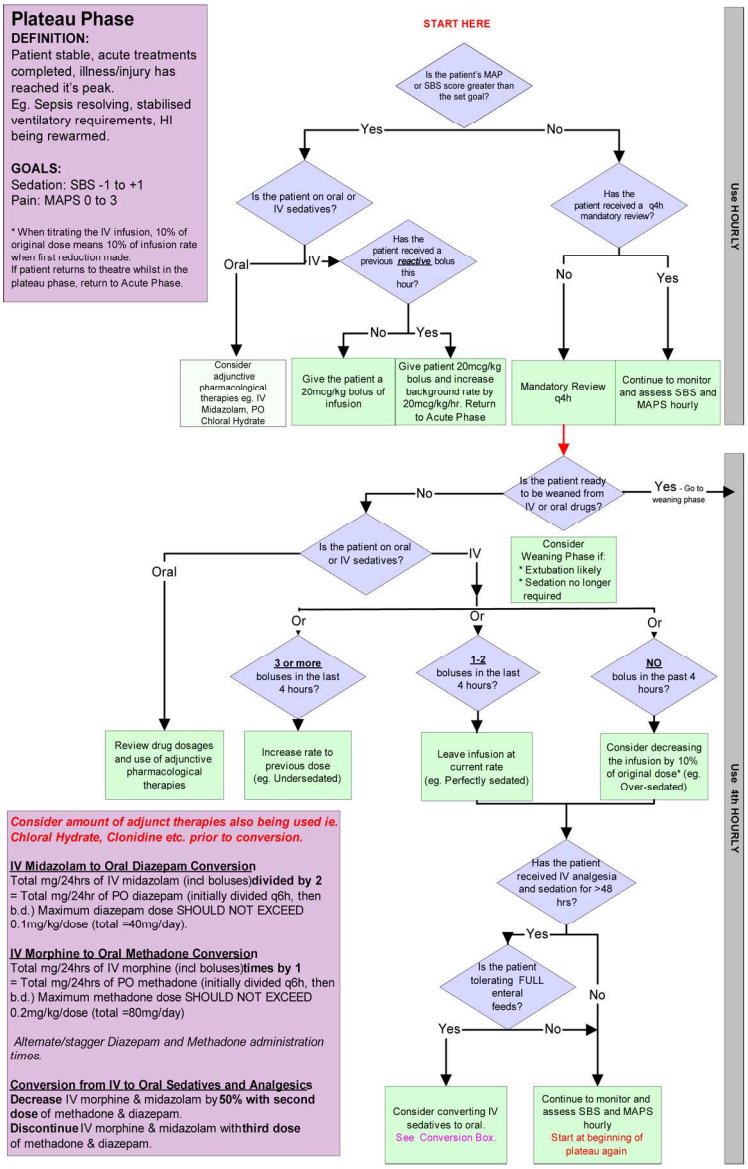

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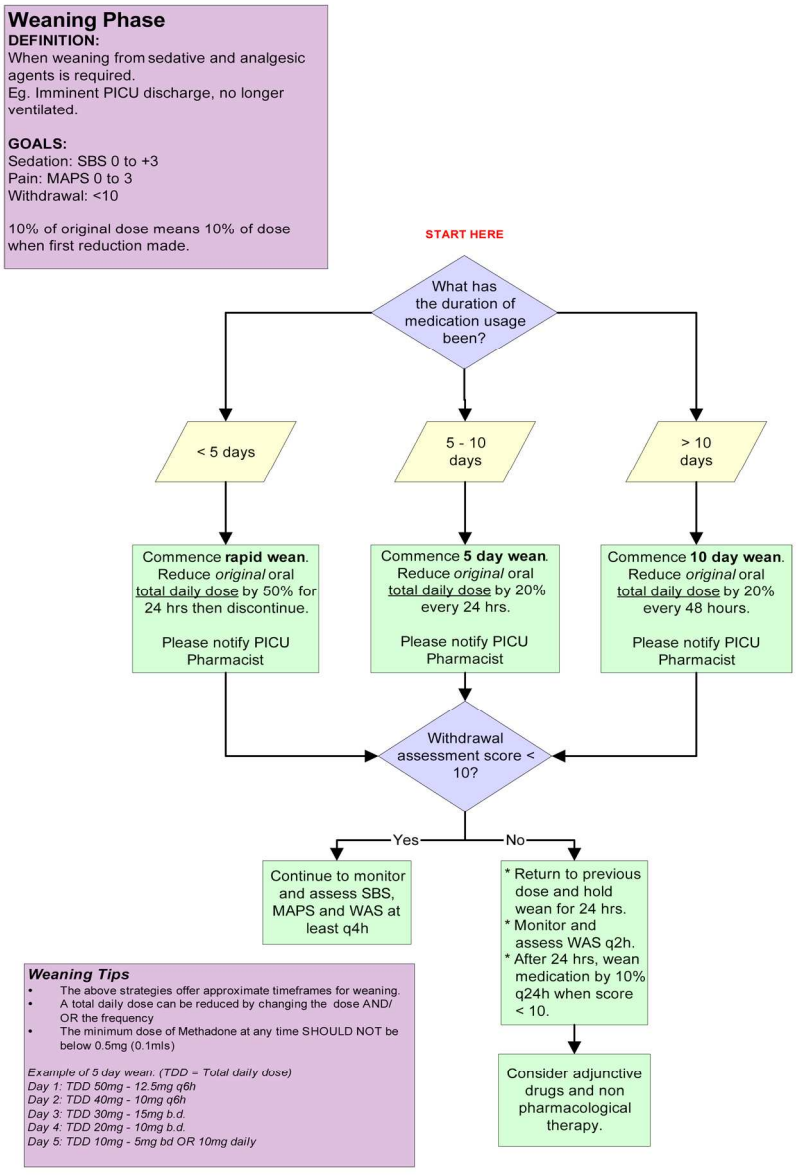

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Practice guidelines for sedation and analgesia management of critically ill children: A pilot study evaluating guideline impact and feasibility in the PICU.

Authors:

Samantha J Keogh [1,3] RN PhD, Debbie A Long [2,3] RN PhD, Desley V Horn [2] RN MSc

[1] Nursing Research Services, Royal Children's Hospital, Brisbane, Queensland, Australia

[2] Paediatric Intensive Care Unit, Royal Children's Hospital, Brisbane, Queensland, Australia

[3]NHMRC Centre of Research Excellence in Nursing (NCREN) - Centre for Health Practice Innovation – Griffith Health Institute, Griffith University, Nathan, Australia

c/- NHMRC Centre of Research Excellence in Nursing

Griffith University, Nathan Campus

170 Kessels Road

Brisbane Qld AUSTRALIA 4111

Tel: +61 7 3735 4886

Fax: +61 7 3735 3560

Email: s.keogh@griffith.edu.au

Keywords: Paediatric Intensive Care, Sedation, Analgesia, Guidelines.

Abstract

Objectives: The aim of this study was to develop, implement and evaluate guidelines for sedation and analgesia management in the paediatric intensive care unit (PICU).

Method: The study used a pre post study design using a historical control.

Setting: The guidelines were trialled in two paediatric intensive care units at different hospitals in an Australian metropolitan city.

Participants: Patients admitted to the PICU and ventilated for ≥24 hours, aged more than one month of age and not admitted for seizure management or terminal care were recruited into the study.

Intervention: A trial of guidelines for sedation and analgesia management for critically ill children including algorithm and assessment tools.

Primary and secondary outcome measures: In addition to key outcome variables (ventilation time, medication dose and duration, length of stay), feasibility outcomes data (recruitment, data collection, safety) were evaluated. Guideline adherence was assessed through chart audit and staff were surveyed about merit and use of guidelines.

Results: The guidelines were trialled for a total of 12 months on 63 patients and variables compared to historical control group (n= 75). Analysis demonstrated significant differences in median Morphine infusion duration between groups (pretetst 3.63 days (87hrs) vs posttest 2.83 days (68hrs), *p=0.05*) and maximum doses (pretest 120mcg/kg/hr vs postest 97.5 mcg/kg/hr) with no significant difference in ventilation duration. Chart audit revealed varied use of tools, but staff were positive about the trial and the perceived impact the guidelines had on practice.

Conclusions: The sedation guidelines in this study appear to be feasible in practice, and impacted on the duration and dosage of agents without adversely impacting on ventilation duration or length of stay. The results of the study have laid foundation for follow on studies in withdrawal from sedation, point prevalence and longitudinal studies of sedation practices as well as drug trial work.

Strengths of study:

- Detailed outline of guideline development process based on consensus paper and available evidence
- Original dual site feasibility (pilot) study testing impact of guidelines on patient, quality and practice outcomes
- Generation of clinical and trial process data to inform future trial work

Limitations of study

- No firm evidence or 'cause and effect' can be concluded due to pre/post study design and small sample size

Funding statement and acknowledgments

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Introduction

Sedation and analgesia are necessary components in the care of all critically ill patients, especially those requiring mechanical ventilation. The main indications for their use include: to reduce patient pain, anxiety and agitation, induce amnesia, facilitate mechanical ventilation, prevent the displacement of endotracheal tubes, and decrease cellular metabolism [1-3]. The detrimental impact of poor sedation practices in intensive care units has increasingly become a focus for researchers and clinicians and extends from concerns for both under sedation to over sedation[4]. Both under and over sedation has the potential to lead to agitated patients with compromised short term safety issues and impact on duration of ventilation and length of stay.[5 6]. The consequences of prolonged use of sedative and analgesic agents in the intensive care unit patient include central nervous system activation, gastrointestinal disturbances, and sympathetic hyperactivity. These signs and symptoms have been related to tolerance and withdrawal phenomena and also hold implications for the patient's physical and psychological well being as well as health care costs [7-9]. These risks are potentially amplified in the critically ill child in the paediatric intensive care unit (PICU) due to the developing brain[10 11]. **The aim of this study was to develop, implement and evaluate guidelines for sedation and analgesia management in the PICU as a part of program of research in this area and as a prelude to future trial work.**

Background

The 2006 consensus guidelines on sedation and analgesia in critically children established a standard for clinical practice in paediatric intensive care units (PICU) [12]. The guidelines' key recommendations include advice on a loading dose and administration for analgesia and sedation medication, the use of validated pain and sedation assessments tools, withdrawal assessment, and the inclusion of non-pharmacological interventions. Surveys of sedation and analgesia management in PICUs have identified a lack of specific protocols for sedation and analgesia management [13-15]. This research has also highlighted wide variations in physician practice, nursing assessment, pharmacological agents, as well as administrative

methods and doses. Limited use of assessment tools has also been reported, and there were no measurements or guidelines for withdrawal of drugs.

Table 1 Summary of 2006 consensus paper recommendations for sedation management of critically ill children.

1. Non pharmacological interventions	i. Any correctable environmental and physical factors causing discomfort should be addressed alongside the introduction of pharmacological agents. ii. A normal pattern of sleep should be encouraged. Attention should be paid to lighting, environmental noise and temporal orientation of patients.
2. Pain assessment and analgesic management	i. All critically ill children have the right to adequate relief of their pain. Local and regional anaesthetic techniques should be considered. A patient controlled analgesia (PCA) device may be useful in older children. ii. Pain assessment should be performed regularly by using a scale appropriate to the age of the patient and routinely documented. The level of pain reported by the patient must be considered the current standard of analgesia. Patients who cannot communicate should be assessed for the presence of pain-related behaviours and physiological indicators of pain. A therapeutic plan for analgesia should be established for each patient and regularly reviewed. iii. Recommended pharmacological agents for analgesia include opioids (e.g. Morphine, Fentanyl) for the relief of severe pain, nonsteroidal anti-inflammatory drugs (NSAIDs) for moderately severe pain, and paracetamol for mild to moderate pain.
3. Sedation assessment and recommended or commonly used sedative agents	i. Adequate analgesia should be provided to all critically ill children regardless of the need for sedation. The use of clinical guidelines for sedation is recommended. ii. The level of sedation should be regularly assessed and documented using a validated and age appropriate sedation assessment scale. The desired level of sedation should be identified for each patient and should be regularly reassessed. Doses of sedative agents should be titrated to produce the desired level of sedation. iii. Recommended pharmacological agents for sedation include Midazolam or Clonidine. Early use of enteral sedative agents (e.g Chloral Hydrate, Promethazine) is recommended. Propofol should not be used to provide continuous sedation in critically ill children.
4. Withdrawal syndrome assessment, prevention	i. The potential for opioid and benzodiazepine withdrawal syndrome should be considered after 7 days of continuous

and management	therapy. ii. When subsequently discontinued, the doses of these agents may need to be routinely tapered.

A number of studies have attempted to evaluate the impact of sedation and analgesia guidelines in PICU, however the results have been varied [16-20]. Each of the studies successively added to our knowledge and understanding of sedation and analgesia management in critically ill children. However, differences in guideline specifics, models of care, and study design may contributed to the varied outcomes observed in the studies and limited their ability to inform best clinical practice. The aim of this study was to develop sedation and analgesia management guidelines based on the 2006 consensus recommendation and test their feasibility and acceptability in practice as a prelude to rigorous trial evaluation of guidelines in practice.

Methods

Aims and Objectives of Study

The main aim of this study was to develop, implement and evaluate locally developed guidelines for sedation and analgesia management on patient outcomes. Secondary aims were to evaluate the feasibility and acceptability of the guidelines in practice.

Study design

This dual site study used a pragmatic pre and post test design to examine the feasibility and impact of the guidelines on patient and practice outcomes. A chart audit was used to assess the implementation fidelity and a (nursing) staff survey was conducted to ascertain staff perceptions of guideline utility and acceptability in practice. The study received full ethical and institutional approval (HREC/05/QRCH/19) The requirement for consent was waived.

Setting

The study units were two eight-bed, mixed medical surgical (not cardiac surgery) PICUs located at tertiary referral children's hospitals admitting patients from 0-16 years of age. Post registration qualifications in either paediatrics, ICU or PICU were held by approximately 48% of the nursing staff.

Sample and Participants

The target population was all patients ventilated for ≥ 24 hours within the PICU, aged more than one month of age and not admitted for seizure management or terminal care. All eligible patients were consecutively enrolled into the study. As the main aim of the study was feasibility rather than hypothesis testing, the statistical power of the sample was of reduced importance. Charts of patients in the post implementation phase were the focus of the audit. All nursing staff were invited to participate in the survey gauging staff perceptions and use of the guidelines in practice.

Guideline development

The sedation and analgesia guidelines for this study were developed around an algorithm for each of the identified phases of sedation (See Appendix 1). The key recommendations of the guidelines developed and tested in this study were based on the key recommendations in the 2006 consensus paper which was summarised in Table 1 [12].

A range of non pharmacological strategies to minimise patient stress and pain, and optimise comfort are supported by varying levels of evidence ranging from case studies to Cochrane systematic reviews. These were not new strategies but it was important to incorporate them into the guidelines to promote a holistic approach to pain and sedation management and reflect the recommendations of the consensus guidelines. Strategies recommended were aimed at moderating the PICU environment where possible (i.e. minimising high intensity light and noise, ensuring rest periods) [21 22]; minimising discomfort of invasive devices; regular repositioning and limb support with pillows, pressure relieving devises or swaddling

[23 24]; monitoring and optimising hydration, nutrition and essential cares (e.g. oral and eye care); supporting parental visitation and reassurance as well as therapeutic (non-technical) touch [25 26].

New assessment scales for behavioural state, pain and withdrawal assessment were integral to the guidelines. These included the State Behaviour Scale (SBS)[27 28], the Multidisciplinary Assessment of Pain Scale (MAPS)[29-32] and the Opioid Benzodiazepine Withdrawal Assessment Scale (WAS) [33 34].

The three phases of sedation (acute, plateau and weaning) management were derived from patterns observed in a retrospective audit conducted earlier by the research team [35 36] and from the literature [9 12 37-39]. The guidelines reflect the dynamic nature of a PICU patient's admission and allow for movement between and within phases according to patient need, response and condition.

As the main aim of the guidelines was to improve consistency in medication practices, it was vital to get a consensus on prescribing practices within the study units. Even the authors of the consensus guidelines note that there is limited evidence to draw on and the recommendations were based on knowledge of drug pharmacokinetics, case study reports, expert opinion, and also the understandings of pain management, drug tolerance and withdrawal medicine. Morphine and Midazolam are the most common analgesic and sedative agents used in PICUs [3 14 40 41] and the drugs of choice in the study units. They are typically used in combination as together they have a synergistic effect that often allows for use of lower doses. Midazolam doses can be reduced as much as 30%-50% when combined with an opioid [42]. Nonetheless, prolonged and/or heavy sedation persists in critical care units, and as a result tolerance and withdrawal syndrome complicate recovery.

In the Acute Phase the guidelines proposed a significant loading dose to achieve the desired analgesia and sedation goals, followed by regular patient assessment and incremental medication changes to achieve and maintain these goals. If the maximum dose allowed was reached (i.e. 300mcg/kg/hr for past 4 hours) then use of adjunct or alternative drugs was recommended (i.e. clonidine, fentanyl). “Drug cycling” has been reported to be helpful in the United Kingdom, where 25% of PICUs surveyed reported rotation of sedatives to minimize tolerance [3]. In another paper, consultant intensivists conducted biweekly chart reviews of each patient in the ICU and regularly change their sedation regimens [43]. Although these authors imply success with drug tolerance, no numerical data was offered in support.

Once in the Plateau phase, the key change in practice was the recommended conversion from intravenous to long acting enteral agents. This approach is based on the principles of narcotic withdrawal where withdrawal syndrome is managed by conversion to an orally active drug with a longer half life (such as methadone or diazepam) that has a more steady state serum concentration, more readily facilitating a slow taper of the drug and minimizing the severity of withdrawal symptoms or even development of withdrawal syndrome [44-47]. The advantages of methadone are an oral bioavailability of 75% to 80% allowing for oral administration, and a prolonged half-life of 12-24 hours, allowing twice daily administration (ibid). There is a general reluctance to use diazepam for critically ill patients because of its long elimination and concerns about excessive and prolonged sedation. However, similar to methadone, diazepam’s long acting active metabolites theoretically should result in small changes in serum drug concentrations and may decrease fluctuations in sedation state and therefore be a more appropriate agent for long term sedated patients [39].

The formal acknowledgement of a Sedation Weaning phase with a dedicated assessment tool and tapering regime was new practice for the study units. No validated opioid or benzodiazepine weaning schedule was found however a consensus of opinion across the literature supports daily reduction of 5% to 10% or an initial reduction of 20% to 40% and

followed by a 10% reduction once or twice daily, depending on patient response [39 48]. The protocol for sedation weaning incorporated into these guidelines approximated these recommendations.

Guideline Implementation

The guidelines encompassed many changes in practice: new assessment scales, standardising of practice, conversion to oral agents, algorithms, and a discreet weaning pathway. In the interest of maximising staff understanding and uptake of the tools, a phased implementation process was adopted with the gradual introduction of each tool into the units, followed by orientation and implementation to the algorithm phases and medication administration. Staff in-services introducing the study and guidelines were held over an initial fortnight with phased introduction and implementation of each assessment tool over the following months. These were further supported by bedside education on tool use and supplemented by information and teaching aids on the units' computer system.

In practice, the PICU team set sedation and analgesia goals as part of the daily patient review and staff at the bedside (usually nurses) used the guidelines to achieve the set goals.

Outcome variables

Data was collected from all eligible patients over 24 months (12 months historical control and 12 months post implementation), plus a break to allow for the implementation period. In addition to the main study outcomes, the pilot study collected outcomes to establish feasibility of the protocol and processes. Feasibility data outcomes included the success of screening and recruitment strategies; data collection and entry processes; confirmation of Research Nurse time and cost, and produce further estimates of ventilation times and medication dosing, that can be used to finalise sample size requirements for the larger trial, and inform funding applications for same. The main study outcomes measured included total ventilation time (TVT), sedation doses and duration, length of stay in the PICU (LOS), plus quality indicators such as, accidental extubation and readmission rates. It was important to

establish that the outcomes were not adversely effected by the guidelines before considering larger and more extensive trial work. Potentially confounding variables collected included patient age, gender, diagnosis, and the Paediatric Index of Mortality (PIM2) as a measure of acuity. Nurses in the study setting routinely collect and record standard demographic and biophysiologic patient measurements on the local computerised information system. The revised paediatric index of mortality (PIM2) is a simple model of mortality in paediatric intensive care based on admission data and uses ten explanatory variables [49]. Post implementation compliance/fidelity was assessed by chart review using an audit tool based the 19 key components of the guidelines. Adherence to 75% of the key components overall and then within each phase was nominally chosen as the minimum acceptable value for fidelity at this stage. However, the results whatever they were would inform any future implementation processes and trial work. Nursing staff perceptions of the guidelines were ascertained through administration of a researcher developed survey with questions on ease of use, impact on practice, perceived benefit, facilitation of team management, and promotion of nurse autonomy at bedside. Staff members were also given the opportunity to comment on strengths and limitations of the guidelines.

Statistical analysis

Data were analysed using PASW 18.0 (SPSS Inc.). Descriptive statistics were used for demographic data. Continuous values reported were medians and ranges due to the large spread of the data. Categorical variables were reported as counts and percentages. Non parametric Mann Whitney or Cross tabulation and Pearson's Chi Square were performed to compare groups. The probability of remaining ventilated between groups was analysed using survival analysis. Adherence to guidelines was reported in counts and percentages. The influence of diagnostic group on guideline adherence was analysed using Pearson's Correlation and comparison of means using student's T-test. Survey responses were reported in counts and percentages as well as significant themes derived from qualitative data.

Results

During the two study periods (12 months each) 173 and 235 patients were ventilated in the respective pre and post guideline implementation periods. After screening for eligibility 75 and 70 patients were enrolled into the pre and post groups. Seven patients were lost to the study in the posttest group because of deviation from research protocol (n=5), one group of parents did not consent to use of the drugs, and one was transferred to another hospital. Ultimately there were 75 in the control group and 63 in the post implementation group. Data were analysed on a *per protocol* basis. Figure 1 demonstrates the sampling framework and exclusion criteria.

INSERT FIGURE 1

Table 2 shows the main characteristics measured for each sample. Both groups were comparable with no significant differences between age, weight, sex, or reason for admission. There were also no significant differences identified between the TVT and LOS for each group. There were no incidents of accidental extubation or readmission within 48 hours for subjects in either group for the study.

Table 3 shows the different drug characteristics between groups, demonstrating a greater variance in drug usage. The decrease of 19 hours in the median infusion time of Morphine between groups approached significance (87hrs vs 68 hrs, *p=0.059*). There were changes in the median minimum and maximum Morphine doses, though not significantly. A reduction of 11 hours was identified with median infusion of Midazolam between groups, however this difference was not significant. Significant changes in the median minimum and maximum doses of Midazolam were observed (MIN 10mcg/kg/hr vs 17 mcg/kg/hr, *p <0.001* and MAX 120mcg/kg/hr vs 180mcg/kg/hr, *p<0.001*).

	Pre n=75	*Post n=63*	*Statistic*
Age (yrs) Median (IQR)	2.08(5.6)	1.75(4.5)	NS Mann Whitney
Weight (kgs) Median (IQR)	11.5(15.62)	12(11)	NS Mann Whitney
Sex No (%)	Male 45(60%)	Male 38(60%)	NS Chi square
Primary Diagnosis No (%)	Resp 29(39%)	Resp 21(33%)	NS Chi square
PIM Median (IQR)	5.00 (9)	5.20 (5.3)	NS Mann Whitney
TVT(days) Median (IQR)	4.02(5.36)	3.12(7.68)	NS Mann Whitney
LOS (days) Median (IQR)	6.3(6.76)	5.8(7.90)	NS Mann Whitney

NS = not statistically significant i.e. p≥0.05

Table 2: Baseline characteristics in the study groups

	Pre n=75 *Median (IQR)*	***Post n=63*** *Median (IQR)*	*Difference and Statistic*
Morphine			
Infusion duration (hrs)	87 (136.5)	68 (78)	-19 hrs *p=0.059*
Min dose (mcg/kg/hr)	10 (11)	17 (10)	+7mcg/kg/hr NS
Max dose (mcg/kg/hr)	120 (102.25)	97.5 (52.75)	-22.5 mcg/kg/hr NS
Midazolam			
Infusion duration (hrs)	71 (154)	60 (90)	-11 hrs NS
Min dose (mcg/kg/hr)	10 (12)	24 (20)	+14 mcg/kg/hr *p<0.001*
Max dose (mcg/kg/hr)	120 (101.75)	180 (143.25)	+60 mcg/kg/hr *p<0.001*

NS = not statistically significant i.e. p≥0.05

Table 3: Outcome variable comparison between study groups

Applying the Kaplan-Meier curve of risk to the probability of remaining ventilated to each group demonstrated that posttest group did not have an increased risk of remaining

ventilated (see Figure 2). The probability of remaining ventilated was reduced in the posttest group (by just less than a day at 21 hours); however this was not statistically significant.

INSERT FIGURE 2

Other significant changes in practice were the greater use of adjunctive and alternative medication, in particular methadone. Results showed that prior to the guideline implementation there was limited use of alternative medications (1-2 alternative medications or even none). Post guideline implementation the numbers of alternative medications used increased. More detailed analysis revealed a significant difference with the use of Methadone pre 3% - post 33% *p<0.001;* Diazepam pre 5% - post 25%, *p=0.001;* Chloral Hydrate pre 32% - post 58% *p=0.002;* Propofol pre 60% - Post 20% *p<0.001;* and Neuromuscular blockade agents pre 60% - post 47.6% *NS.*

Implementation fidelity (Chart Audit)

Sixty-three charts from the post implementation period were reviewed to identify the level of staff adherence to the 19 key components of the guidelines and quantify the level of assessment and scoring. Overall adoption was achieved in 23 (36%) of the charts audited. Separate analysis within each of the phases demonstrated that adoption was achieved in 30 (47.6%) in the acute phase, 23 (36.5%) in plateau, and 25 (39.7%) in the weaning phase. Pain and sedation scores were assessed and documented in 95% (n=60) of charts in the acute and plateau phases, and 85% (n=54) of charts in the weaning phase. The withdrawal score was assessed and documented appropriately in 75% (n=47) of charts.

Staff survey

The response rate was 49% (n=54). Participants' responses were divided into four categories: awareness/use, strengths, limitations and suggestions for improvement. Fifty-two (96%) staff regularly referred to the guideline to assist with decision making and to provide

prompts and cues. There appeared to be some confusion as to who was primarily responsible for the initiation of the guidelines, with 12(23%) suggesting is was the consultants' responsibility and 32(60%) stating it was the bedside nurse. Table 4 outlines further responses.

Questions	***Yes Response n=54***
The sedation guidelines and flowchart are easy to follow	58.5%
The flowchart facilitates the sedation management process	87%
Patients benefit from having a constructive escalation program	96.3%
Patients benefit from having a constructive titration program	94.3%
Patients benefit from having a constructive weaning program	96.2%
A multidisciplinary approach enhances sedation management	96.3%
The guidelines give me more autonomy in managing sedation	68.5%
The guidelines improve overall sedation management	88.5%

Table 4: Staff perceptions of sedation guidelines in practice

Perceived strengths of the tool included the structured nature of the guidelines, promotion of consistency in practice and the resulting increased awareness regarding sedation management. Conversely perceived limitations included the perceived complexity of algorithm, confusion with delineation and movement between phases, and the lack of accommodation of increased drug tolerance with long term patients. Staff suggested simplifying the algorithm and using larger print, incorporating recommendations for short term patients and providing clinical example as guides. . Table 5 provides the staff comments on perceived strengths and weaknesses of the guidelines Overall four major themes were expressed by study participants (see table 5): (1) a knowledge deficit about some aspects of the guidelines, (2) high value placed on individualised patient care, (3) perceived ineffectiveness of the guidelines for some patients, and (4) disagreement between doctors and nurses on responsibilities.

Strengths
▪ The bedside nurse 'knows' the patient and their requirements, can initiate changes, use objective data on the screen, can see changes and ask for review if needed. ▪ It is a clinical tool to justify an increase or decrease in sedation. Allows for uniform/consistent decision making. ▪ Empowers and rationalises nursing changes in sedation. ▪ Everyone using the same guide should translate to more consistent care. There is more autonomy for nurses, particularly with less experienced registrars. It potentially irons out variations in individual consultant preferences. ▪ It has increased the awareness amongst staff and prompts discussion. ▪ It places importance on sedation and assists nurses to provide better sedation. Patients more comfortable equals parents more comfortable.
Limitations
▪ Can be complicated because of the amount of detail. ▪ Needs definitions and differential diagnoses for each of the phases. ▪ Not all patients fit the guidelines or respond as predicted. ▪ Requires full concentration with attention to detail and practice to become familiar. ▪ Lack of medical leadership/ownership shared. ▪ Difficult to continue in ward, particularly with weaning. ▪ Have trouble with some long term patients following the guidelines and keeping them comfortable.

Table 5: Staff perceptions of strengths and limitations of sedation guidelines.

Discussion

This pragmatic study demonstrated that the guidelines were feasible and acceptable in practice. The use of guideline directed sedation and analgesia management allowed the PICU team to achieve the patient's sedation goals quicker without significantly increasing ventilation times or PICU length of stay. Full adoption of all aspects of guidelines was not realised but results demonstrated improved levels of patient assessment, increased use of enteral agents, and largely positive feedback on guidelines in practice.

The observed increases in median minimum and maximum doses of Morphine and Midazolam do not seem to have increased patient TVT or LOS, and in fact the duration of each infusion was reduced, significantly in the case of Morphine. Similar changes in medication administration were observed in other PICU guideline studies [16-20].

The results of Kaplan-Meier Risk analysis demonstrate that there was reduced risk of remaining ventilated in the post-test group though this was not statistically significant. However, a median difference of 21 hours between groups may be viewed as 'clinically significant' as this time difference in the clinical setting could translate to earlier extubation and/or discharge. A reduction in ventilator duration was also observed in two other studies. Larger, randomised trial studies are warranted to further explore this important outcome.

Only a small proportion of participants were ultimately eligible for the study (43% and 31% respectively), which has implications for the projected timeline, research assistant time and costs and data collection for a larger multi site trial. The results also revealed the huge spread of the clinical data and the challenge this posed for researchers. Follow on studies would possibly need to consider subcategories of patients i.e. short, medium and long term ventilated and analysing within these categories.

The guidelines and implementation process in this study also appear to have significantly increased awareness and usage of alternative medications to complement or replace the Morphine/Midazolam. This was particularly evident with the use of Methadone and Diazepam. Use of Methadone rose from 3% pre test to 33% post test. Use of Diazepam rose for 5% pre test to 25% post test. One of the key recommendations to emerge from the literature and therefore included in the guidelines was the transition from continuous intravenous analgesia and sedation to regular oral agents. Prolonged administration of opioids and benzodiazpines may result in the development of drug tolerance and then withdrawal syndrome if these agents are abruptly discontinued [9 38 50 51]. Research has shown that this can be prevented by slowly tapering the intravenous administration of the drug or switching from intravenous morphine and midazolam to orally active drugs with a longer half-life, such as methadone and diazepam [45 47]. In general the increased use of adjunct medication was evidence of the clinician use of guideline recommendations.

Sedation, Pain and Withdrawal scores were all captured but difficult to summarize meaningfully as a research variable. We recommended that a useful variable for follow in studies be to calculate the percentage of time each patient spent in a designated 'zone' and determining appropriateness and success /failure of management accordingly.

The audit of implementation fidelity demonstrated that the assessment and documentation of patient's pain and sedation was well recorded, reflecting sound staff understanding and uptake of the new assessment tools. The adoption score for the withdrawal phase was the lowest of the three phases, which may have resulted from less familiarity and knowledge with the tool and phase. This is consistent with findings were found in a review of similar studies [52]. Suggested reasons for non-adherence included complexity of guideline or algorithm, staff not valuing or understanding goal of guideline, perceived redundancy of guideline if staff already competent practitioners in this area (ibid). Potential solutions to these issue included ongoing staff education and timely feedback related to the guideline to continuously reinforce importance, ease of use, and troubleshoot issues[53]. In addition to surveying staff opinion, it is also important to conduct periodic chart audits to quantify guideline fidelity. This will help minimise self-report bias as was somewhat reflected in this study[54]. Staff perceptions of guideline principles and use were positive although level of adherence variable. So the full impact of the guidelines were not realised.

In conjunction with the audit, a survey of staff perceptions and attitudes were undertaken to establish if these influenced adoption of the guidelines. In line with other similar studies, staff were largely positive and constructive in their feedback[18 55 56]. All feedback has been utilised to improve the guidelines. Engaging staff and providing feedback during the process of procedural change is a vital step in optimising follow trial success and ultimately translation to practice.

The importance of the findings of this study are that they demonstrate that collaborative guidelines for sedation management can optimise the PICU patient's sedation and analgesia management without compromising quality of care (TVT, LOS, quality indicators). The results are similar to those in the adult population where guideline or protocol driven sedation has been linked to a reduction in duration of continuous intravenous sedation, ventilation time and associated health care costs [57-61]. Evaluation of feasibility outcomes has aided in development a realistic plan about participant recruitment, staff education to optimise guideline fidelity, safety of guidelines in clinical practice and collection of key outcome variables.

Implications & Recommendations

No definitive causal effect can be attributed to the guidelines on outcomes due to the pre post study design and small sample size. Full adoption of all phases and tools in the guidelines was not realised and this has implications for ongoing implementation and larger trial work. Additionally the small response rate and selective population for the survey may introduce some bias in the current understanding of staff acceptance of the guidelines. A more inclusive (medical and nursing) survey population is recommended for follow research. Conducting the study in two units assists with the generalisability of the study and its results. Some specifics of the guidelines and algorithm, however, might need modification to reflect local practice. For example, use of different drugs (fentanyl instead of morphine) and different patient populations (post cardiothoracic surgery).

The study results are most useful in informing the structure and outcome measures for a follow on clinical trial in this area.

Results from the study, audit and survey have informed changes and modifications to optimise staff understanding and use of sedation guidelines in practice. Weaning from sedation agents and the concept of withdrawal appear to be areas of practice that need more attention. The researchers went on to trial and evaluate a revised withdrawal assessment

tool and a study comparing the outcomes of Dexmedetomidine versus Midazolam is about to commence. The study units plan to continue to use the guidelines and tools in their modified form pending the results of larger trial work recently completed in the USA. The modern ICU is an important focus for quality improvement efforts. Guidelines cannot automatically guarantee improved quality of care; however, they do direct the clinician in the pursuit of this objective particularly when supported by high level evidence.

Contributorship statement:

All three authors, Samantha Keogh, Debbie Long and Desley Horn meet the key three ICMJE guidelines for authorship with each having made (a) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content; and (c) final approval of the version to be published.

Competing interests

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Data sharing statement

A copy of the guidelines can made available by emailing Debbie.Long2@health.qld.gov.au.

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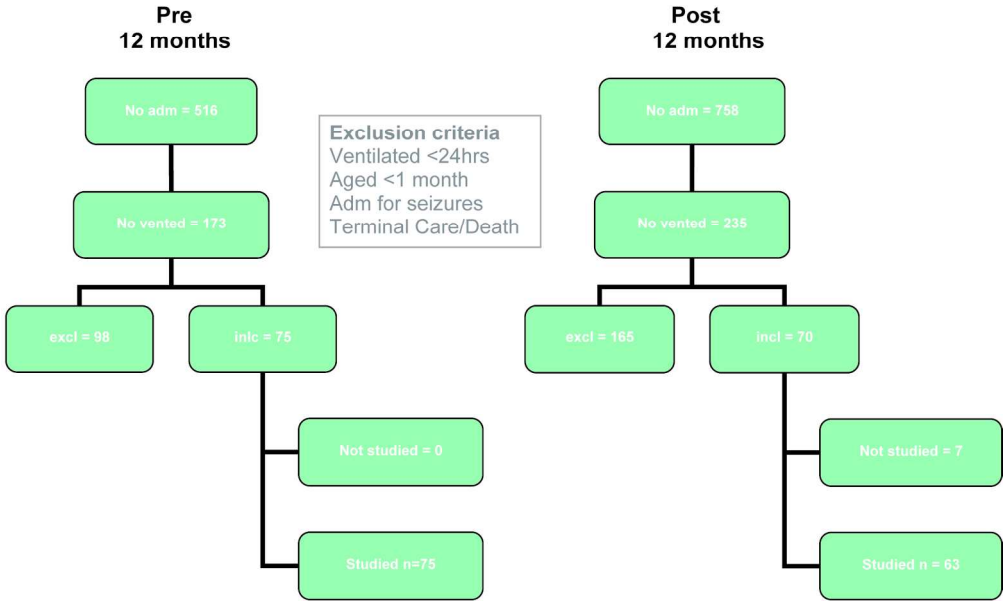
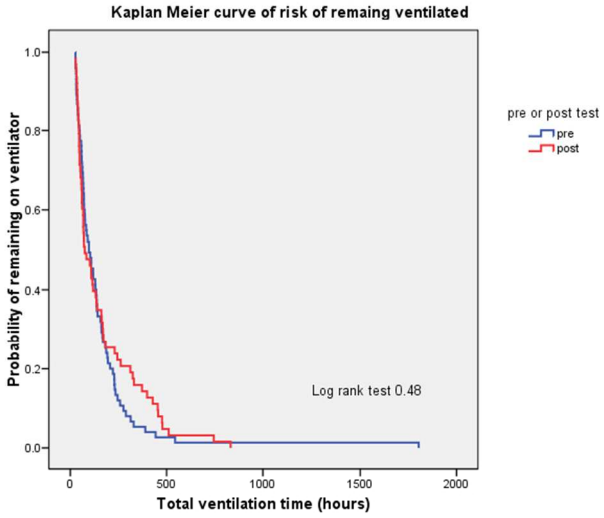
Figure 1: Sample framework



172x113mm (300 x 300 DPI)

Figure 2: Kaplan-Meier Curve of risk of remaining ventilated between groups



209x297mm (98 x 98 DPI)

GUIDELINES FOR THE ADMINISTRATION OF SEDATION AND ANALGESIA IN MECHANICALLY VENTILATED CHILDREN

PURPOSE:
To outline the management of sedation and analgesia in critically ill children receiving mechanical ventilation.

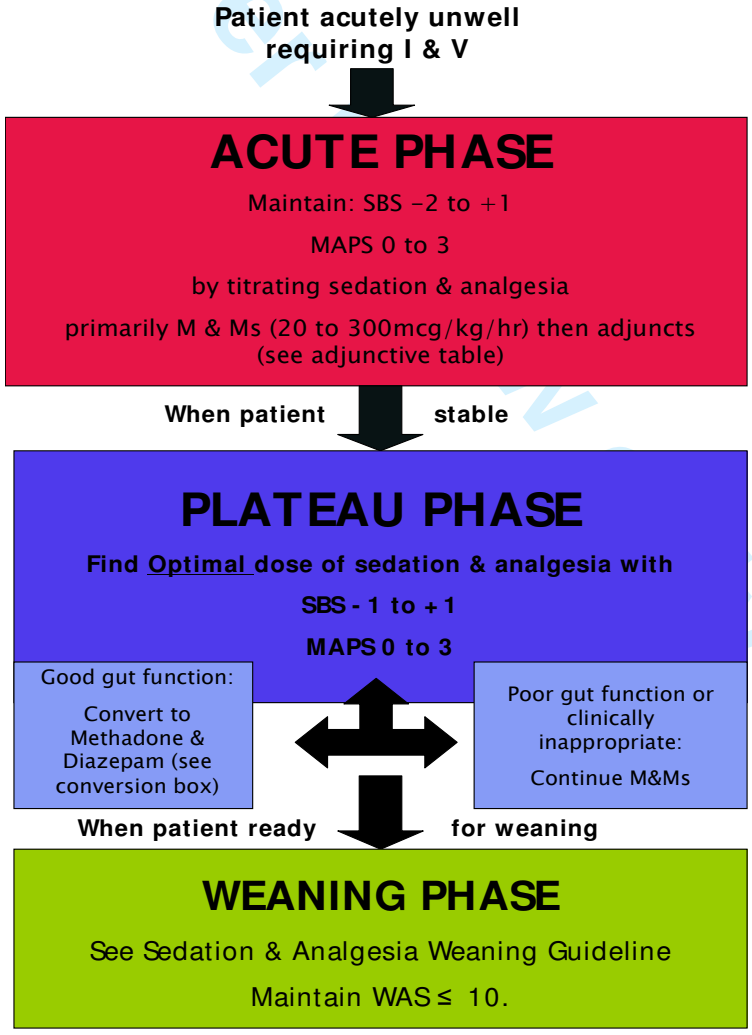
BACKGROUND / SUPPORTIVE DATA:
Sedation and analgesia are necessary components of the care of all critically ill children, especially those requiring mechanical ventilation. The main indications for the use of sedation and analgesia include: to reduce pain and discomfort, to reduce anxiety and agitation, to induce amnesia, to facilitate mechanical ventilation, to prevent the displacement of endotracheal tubes, and to decrease cellular metabolism. The consequences of prolonged use of sedative and analgesic agents in the PICU patient include central nervous system activation, gastrointestinal disturbances, and sympathetic hyperactivity. These signs and symptoms have been related to tolerance and withdrawal phenomena and hold implications for the patient's physical and psychological well being as well as health care costs.

Tolerance is one of the major reported adverse effects associated with continuous benzodiazepine infusions. Tolerance may be defined as a decrease in the effectiveness of a drug after prolonged use or as the requirement of larger doses to achieve the same effect. This phenomenon is due to an adaptation of neuronal cells and not a change of metabolism of the drug. One method of addressing this adverse effect, drug tolerance, is to recognise its occurrence and introduce alternative sedation agents titrated to an accepted sedation level.

A second adverse effect of the prolonged use of analgesic and sedation agents is withdrawal or abstinence syndrome. In paediatric patients, withdrawal syndrome is due to the development of tolerance to sedation and analgesic drugs not dependence or addiction. Studies have shown a strong positive correlation between large total doses of midazolam and the occurrence of withdrawal symptoms. Local, national and international audits have all shown that drug tapering is conducted in very few patients and that most patients have their sedation and analgesic agents abruptly discontinued. Thus, the incidence of withdrawal symptoms may be related to the infrequent tapering of sedation and analgesic agents.

There exists a plethora of literature discussing the adverse effects of sedation and analgesia in the critical care environment, particularly its prolonged use. There appears to be a consensus about the need and benefits of a systematic and coordinated approach to sedation administration, tapering and titration in the PICU.

SUMMARY OF SEDATION ALGORITHM:



EVIDENTIARY TABLE:

Strategy	Evidence
Use of protocol	The use of protocol directed sedation can reduce the duration of mechanical ventilation, ICU and hospital stay and can result in safe, cost-effective improvements.[1-5]
SBS – Sedation Scale	Reliable and valid scale for use in paediatric critical care.[6-8]
PICU MAPS – Pain Scale	Reliable and valid scale for use in paediatric critical care, particularly pre-verbal children.[9-12]
Withdrawal Assessment Scale	Combination of validated tool and Great Ormond Street Hospital protocol[13-18]
Accumulative dose	Up to 300 mcg/kg/hr for Midazolam
Weaning timeframes	[13, 19]
Mandatory review	[20]
Conversion to oral drugs	Diazepam, Methadone [24-26]

SUGGESTED PHARMACOLOGICAL TREATMENT OF PROCEDURAL PAIN AND DISCOMFORT:

Drug Group	Drug	Indications	Evidence
Topical Local Anaesthetic	Angel Cream EMLA	PIV/IAL insertion Venepuncture Arterial Stab Portacath access Lumbar puncture* CVL/ICC insertion*	[1-5]
	Lignocaine 2% & Chlorhexidine 0.05%	IDC insertion	[6, 7]
	Lignocaine 4%	Bronchoscopy*	[8, 9]
Sub-cutaneous injection	Lignocaine 1%	ICC/CVL insertion*	[2]
Disassociative Agent	Ketamine	CVL/ICC insertion Gastroenterology procedure Bronchoscopy Bone marrow aspiration Wound management procedure	[10, 11]
Short acting anaesthetic agent	Propofol	CVL/ICC insertion Gastroenterology procedure Bronchoscopy Bone marrow aspiration	[10, 12]
Short acting sedative & analgesic agent	Morphine & Midazolam	ETT Suctioning Movement/Position change	[30]

* used in conjunction with other drugs

SUGGESTED NON-PHARMACOLOGICAL MEASURES FOR OPTIMISING PATIENT COMFORT

Treatment	Evidence
Positioning & body support	[13-16]
Reassurance by staff and/or parents	[14]
Minimise discomfort of invasive devices (e.g. ETT, CVLs, and drainage tubes).	[14]
Optimise hydration, nutrition, essential cares (e.g. mouth, eye).	[17-19]
Massage, or rocking	[20, 21]
Swaddling	[22-24]
Non-nutritive sucking	[25-27]
Decrease external stimuli (noise, light, movement or handling)	[15, 28, 29]
Music therapy	[20]

SUGGESTED ADJUNCTIVE PHARMACOLOGICAL THERAPIES FOR MAXIMISING PATIENT COMFORT

Drug	Approach	Evidence
Propofol	2.5-3.5mg/kg stat then 7.5-15mg/kg/hr[30] ; 4-6mg/kg/hr[31]	[30-34]
Morphine	20mcg/kg prn	[30]
Midazolam	20mcg/kg prn	[30]
Ketamine	1mg/kg/hr	[30, 32, 33, 35]
Chloral Hydrate	25mg/kg q6h[36] maximum 5g	[35, 36]
Fentanyl	If allergic or renal failure 5-10mcg/kg/hrl	[30, 34, 35]
Promethazine	Oral 0.5mg/kg q6h Maximum 1mg/kg	[37]
Chlorpromazine	0.25-1mg/kg/q6-8h	
Clonidine	3-5mcg/kg q8h	[30, 35, 36, 38]
Haloperidol	0.1mg/kg- 0.1mg/kg q12h	[39]
Phenobarb	5mg/kg/day	[36]
Paracetamol	90mg/kg/24hrs- accumulation in hepatotoxic in pts with impaired LF-	[30]
Codeine	Max 1mg/kg/dose	[30]
Ibuprofen	10mg/kg q6h Precautions- asthma, renal impairment, under 6mths	[30]

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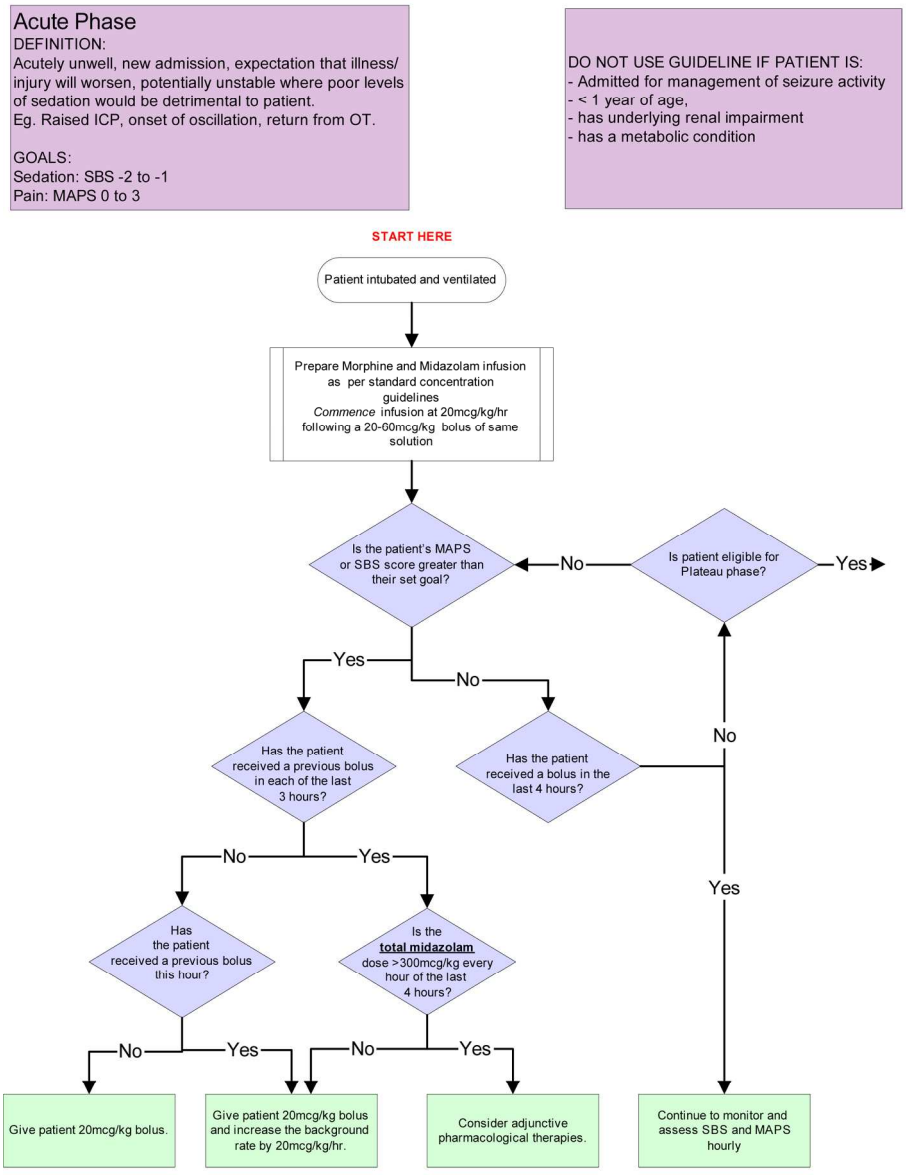

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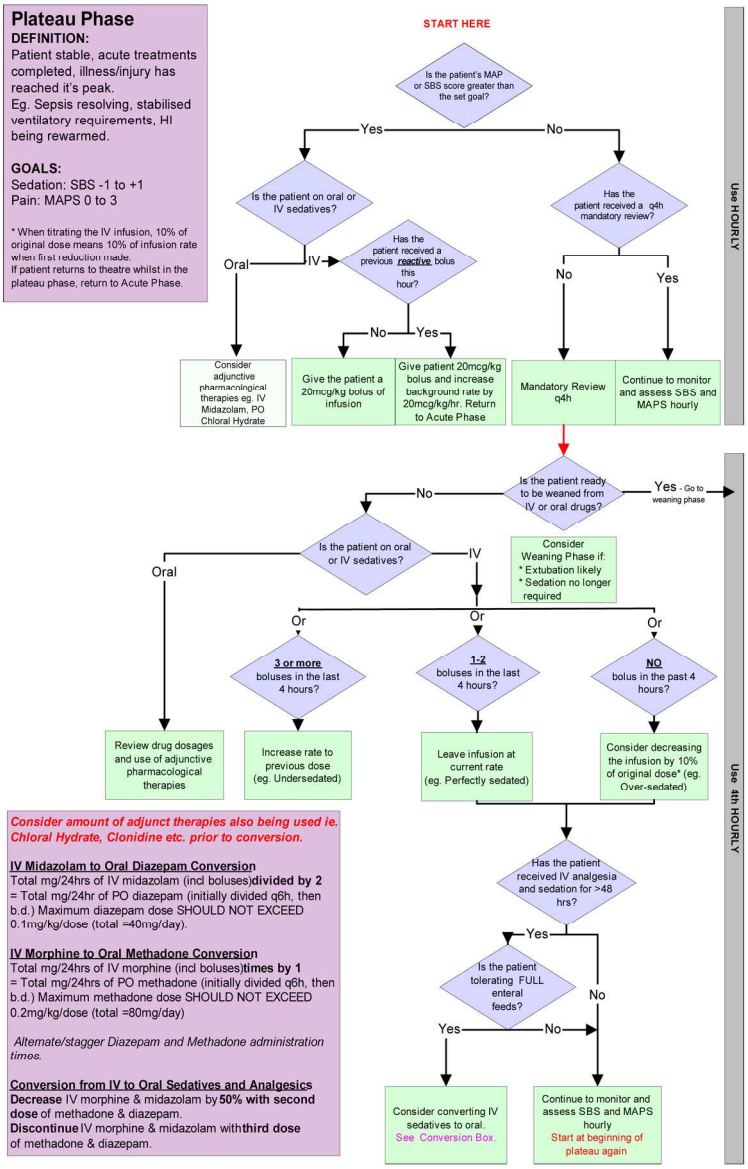

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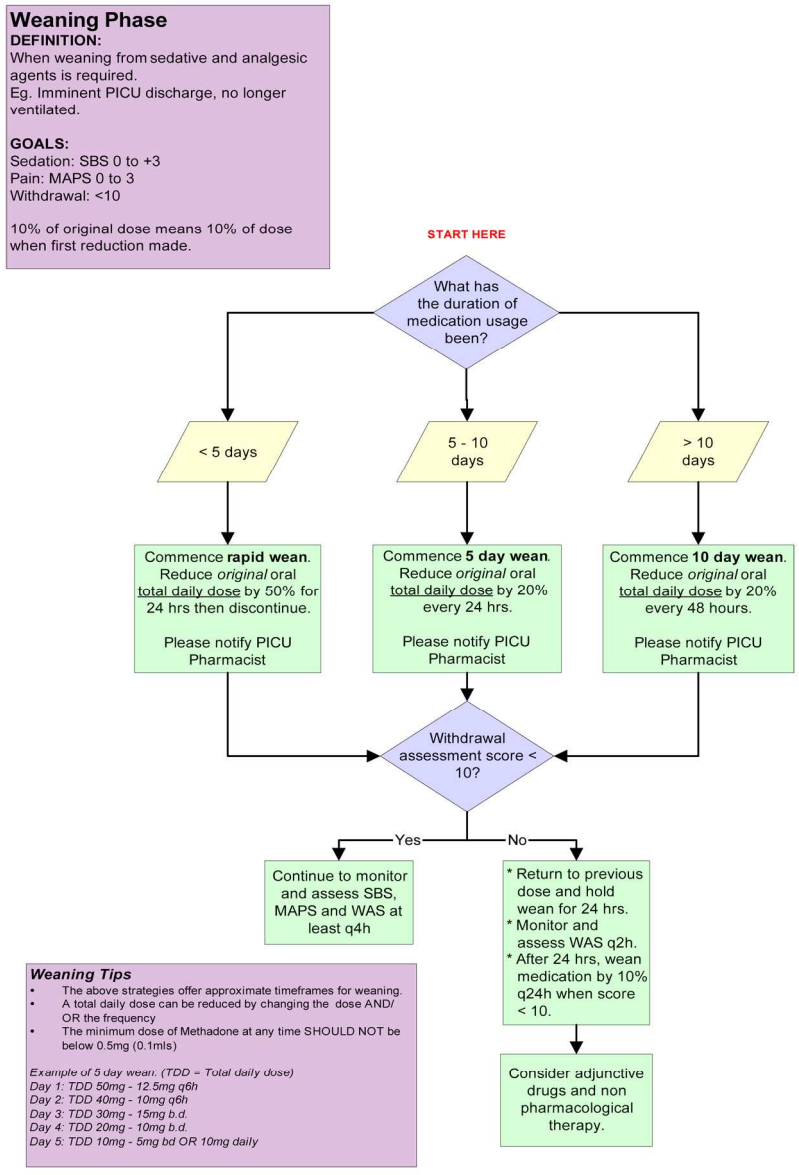

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Practice guidelines for sedation and analgesia management of critically ill children: A pilot study evaluating guideline impact and feasibility in the PICU.

Authors:

Samantha J Keogh [1,3] RN PhD, Debbie A Long [2,3] RN PhD, Desley V Horn [2] RN MSc

[1] Nursing Research Services, Royal Children's Hospital, Brisbane, Queensland, Australia

[2] Paediatric Intensive Care Unit, Royal Children's Hospital, Brisbane, Queensland, Australia

[3]NHMRC Centre of Research Excellence in Nursing (NCREN) - Centre for Health Practice Innovation – Griffith Health Institute, Griffith University, Nathan, Australia

c/- NHMRC Centre of Research Excellence in Nursing

Griffith University, Nathan Campus

170 Kessels Road

Brisbane Qld AUSTRALIA 4111

Tel: +61 7 3735 4886

Fax: +61 7 3735 3560

Email: s.keogh@griffith.edu.au

Keywords: Paediatric Intensive Care, Sedation, Analgesia, Guidelines.

Abstract

Aims: The aim of this study was to develop and implement guidelines for sedation and analgesia management in the PICU and evaluate the impact, feasibility and acceptability of these as a part of program of research in this area and as a prelude to future trial work.

Method: This pilot study used a pre post design using a historical control.

Setting: Two PICUs at different hospitals in an Australian metropolitan city.

Participants: Patients admitted to PICU and ventilated for ≥24 hours, aged more than one month of age and not admitted for seizure management or terminal care.

Intervention: Guidelines for sedation and analgesia management for critically ill children including algorithm and assessment tools.

Outcome variables: In addition to key outcome variables (ventilation time, medication dose and duration, length of stay), feasibility outcomes data (recruitment, data collection, safety) were evaluated. Guideline adherence was assessed through chart audit and staff were surveyed about merit and use of guidelines.

Results: The guidelines were trialled for a total of 12 months on 63 patients and variables compared to historical control group (n= 75). Analysis revealed differences in median Morphine infusion duration between groups (pretetst 3.63 days (87hrs) vs posttest 2.83 days (68hrs), *p=0.05*) and maximum doses (pretest 120mcg/kg/hr vs postest 97.5 mcg/kg/hr) with no apparent change to ventilation duration. Chart audit revealed varied use of tools, but staff were positive about the guidelines and their use in practice.

Conclusions: The sedation guidelines impacted on the duration and dosage of agents without any apparent impact on ventilation duration or length of stay. Furthermore, the guidelines appeared to be feasible and acceptable in clinical practice. The results of the study have laid foundation for follow on studies in withdrawal from sedation, point prevalence and longitudinal studies of sedation practices as well as drug trial work.

Strengths of study:

- Detailed outline of guideline development process based on consensus paper and available evidence
- Original dual site feasibility (pilot) study testing impact of guidelines on patient, quality and practice outcomes
- Generation of clinical and trial process data to inform future trial work

Limitations of study

- No firm evidence or 'cause and effect' can be concluded due to pre/post study design and small sample size

Funding statement and acknowledgments

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Introduction

Sedation and analgesia are necessary components in the care of all critically ill patients, especially those requiring mechanical ventilation. The main indications for their use include: to reduce patient pain, anxiety and agitation, induce amnesia, facilitate mechanical ventilation, prevent the displacement of endotracheal tubes, and decrease cellular metabolism [1-3]. The detrimental impact of poor sedation practices in intensive care units has increasingly become a focus for researchers and clinicians and extends from concerns for both under sedation to over sedation[4]. Both under and over sedation has the potential to lead to agitated patients with compromised short term safety issues and impact on duration of ventilation and length of stay.[5 6]. The consequences of prolonged use of sedative and analgesic agents in the intensive care unit patient include central nervous system activation, gastrointestinal disturbances, and sympathetic hyperactivity. These signs and symptoms have been related to tolerance and withdrawal phenomena and also hold implications for the patient's physical and psychological well being as well as health care costs [7-9]. These risks are potentially amplified in the critically ill child in the paediatric intensive care unit (PICU) due to the developing brain[10 11]. The aim of this study was to develop and implement guidelines for sedation and analgesia management in the PICU and evaluate the impact, feasibility and acceptability of these as a part of program of research in this area and as a prelude to future trial work.

Background

The 2006 consensus guidelines on sedation and analgesia in critically children established a standard for clinical practice in paediatric intensive care units (PICU) [12]. The guidelines' key recommendations include advice on a loading dose and administration for analgesia and sedation medication, the use of validated pain and sedation assessments tools, withdrawal assessment, and the inclusion of non-pharmacological interventions. Surveys of sedation and analgesia management in PICUs have identified a lack of specific protocols for sedation and analgesia management [13-15]. This research has also highlighted wide variations in

physician practice, nursing assessment, pharmacological agents, as well as administrative methods and doses. Limited use of assessment tools has also been reported, and there were no measurements or guidelines for withdrawal of drugs.

Table 1 Summary of 2006 consensus paper recommendations for sedation management of critically ill children.

1. Non pharmacological interventions	i.	Any correctable environmental and physical factors causing discomfort should be addressed alongside the introduction of pharmacological agents.
	ii.	A normal pattern of sleep should be encouraged. Attention should be paid to lighting, environmental noise and temporal orientation of patients.
2. Pain assessment and analgesic management	i.	All critically ill children have the right to adequate relief of their pain. Local and regional anaesthetic techniques should be considered. A patient controlled analgesia (PCA) device may be useful in older children.
	ii.	Pain assessment should be performed regularly by using a scale appropriate to the age of the patient and routinely documented. The level of pain reported by the patient must be considered the current standard of analgesia. Patients who cannot communicate should be assessed for the presence of pain-related behaviours and physiological indicators of pain. A therapeutic plan for analgesia should be established for each patient and regularly reviewed.
	iii.	Recommended pharmacological agents for analgesia include opioids (e.g. Morphine, Fentanyl) for the relief of severe pain, nonsteroidal anti-inflammatory drugs (NSAIDs) for moderately severe pain, and paracetamol for mild to moderate pain.
3. Sedation assessment and recommended or commonly used sedative agents	i.	Adequate analgesia should be provided to all critically ill children regardless of the need for sedation. The use of clinical guidelines for sedation is recommended.
	ii.	The level of sedation should be regularly assessed and documented using a validated and age appropriate sedation assessment scale. The desired level of sedation should be identified for each patient and should be regularly reassessed. Doses of sedative agents should be titrated to produce the desired level of sedation.
	iii.	Recommended pharmacological agents for sedation include Midazolam or Clonidine. Early use of enteral sedative agents (e.g Chloral Hydrate, Promethazine) is recommended. Propofol should not be used to provide continuous sedation in critically ill children.

4. Withdrawal syndrome assessment, prevention and management	i. The potential for opioid and benzodiazepine withdrawal syndrome should be considered after 7 days of continuous therapy. ii. When subsequently discontinued, the doses of these agents may need to be routinely tapered.

A number of studies have attempted to evaluate the impact of sedation and analgesia guidelines in PICU, however the results have been varied [16-20]. Each of the studies successively added to our knowledge and understanding of sedation and analgesia management in critically ill children. However, differences in guideline specifics, models of care, and study design may contributed to the varied outcomes observed in the studies and limited their ability to inform best clinical practice. The aim of this study was to develop sedation and analgesia management guidelines based on the 2006 consensus recommendation and test their impact of patient outcomes as well as feasibility and acceptability in practice as a prelude to rigorous trial evaluation of guidelines in practice.

Methods

Aims and Objectives of Study

The aim of this study was to develop and implement guidelines for sedation and analgesia management in the paediatric intensive care unit (PICU), and following this evaluate the impact, and acceptability feasibility of their use in the clinical setting.

Study design

This dual site study used a pragmatic pre and post test design to examine the feasibility and impact of the guidelines on patient and practice outcomes. A chart audit was used to assess the implementation fidelity and a (nursing) staff survey was conducted to ascertain staff perceptions of guideline utility and acceptability in practice. The study received full ethical and institutional approval (HREC/05/QRCH/19) The requirement for consent was waived.

Setting

The study units were two eight-bed, mixed medical surgical (not cardiac surgery) PICUs located at tertiary referral children's hospitals admitting patients from 0-16 years of age. Post registration qualifications in either paediatrics, ICU or PICU were held by approximately 48% of the nursing staff.

Sample and Participants

The target population was all patients ventilated for ≥ 24 hours within the PICU, aged more than one month of age and not admitted for seizure management or terminal care. All eligible patients were consecutively enrolled into the study. As the main aim of the study was feasibility and acceptability of guidelines rather than hypothesis testing, the statistical power of the sample was of reduced importance at this stage. Charts of patients in the post implementation phase were the focus of the audit. All nursing staff were invited to participate in the survey gauging staff perceptions and use of the guidelines in practice.

Guideline development

The sedation and analgesia guidelines for this study were developed around an algorithm for each of the identified phases of sedation (See Appendix 1). The key recommendations of the guidelines developed and tested in this study were based on the key recommendations in the 2006 consensus paper which was summarised in Table 1 [12].

A range of non pharmacological strategies to minimise patient stress and pain, and optimise comfort are supported by varying levels of evidence ranging from case studies to Cochrane systematic reviews. These were not new strategies but it was important to incorporate them into the guidelines to promote a holistic approach to pain and sedation management and reflect the recommendations of the consensus guidelines. Strategies recommended were aimed at moderating the PICU environment where possible (i.e. minimising high intensity light and noise, ensuring rest periods) [21 22]; minimising discomfort of invasive devices;

regular repositioning and limb support with pillows, pressure relieving devises or swaddling [23 24]; monitoring and optimising hydration, nutrition and essential cares (e.g. oral and eye care); supporting parental visitation and reassurance as well as therapeutic (non-technical) touch [25 26].

New assessment scales for behavioural state, pain and withdrawal assessment were integral to the guidelines. These included the State Behaviour Scale (SBS)[27 28], the Multidisciplinary Assessment of Pain Scale (MAPS)[29-32] and the Opioid Benzodiazepine Withdrawal Assessment Scale (WAS) [33 34].

The three phases of sedation (acute, plateau and weaning) management were derived from patterns observed in a retrospective audit conducted earlier by the research team [35 36] and from the literature [9 12 37-39]. The guidelines reflect the dynamic nature of a PICU patient's admission and allow for movement between and within phases according to patient need, response and condition.

As the main aim of the guidelines was to improve consistency in medication practices, it was vital to get a consensus on prescribing practices within the study units. Even the authors of the consensus guidelines note that there is limited evidence to draw on and the recommendations were based on knowledge of drug pharmacokinetics, case study reports, expert opinion, and also the understandings of pain management, drug tolerance and withdrawal medicine. Morphine and Midazolam are the most common analgesic and sedative agents used in PICUs [3 14 40 41] and the drugs of choice in the study units. They are typically used in combination as together they have a synergistic effect that often allows for use of lower doses. Midazolam doses can be reduced as much as 30%-50% when combined with an opioid [42]. Nonetheless, prolonged and/or heavy sedation persists in critical care units, and as a result tolerance and withdrawal syndrome complicate recovery.

In the Acute Phase the guidelines proposed a significant loading dose to achieve the desired analgesia and sedation goals, followed by regular patient assessment and incremental medication changes to achieve and maintain these goals. If the maximum dose allowed was reached (i.e. 300mcg/kg/hr for past 4 hours) then use of adjunct or alternative drugs was recommended (i.e. clonidine, fentanyl). “Drug cycling” has been reported to be helpful in the United Kingdom, where 25% of PICUs surveyed reported rotation of sedatives to minimize tolerance [3]. In another paper, consultant intensivists conducted biweekly chart reviews of each patient in the ICU and regularly change their sedation regimens [43]. Although these authors imply success with drug tolerance, no numerical data was offered in support.

Once in the Plateau phase, the key change in practice was the recommended conversion from intravenous to long acting enteral agents. This approach is based on the principles of narcotic withdrawal where withdrawal syndrome is managed by conversion to an orally active drug with a longer half life (such as methadone or diazepam) that has a more steady state serum concentration, more readily facilitating a slow taper of the drug and minimizing the severity of withdrawal symptoms or even development of withdrawal syndrome [44-47]. The advantages of methadone are an oral bioavailability of 75% to 80% allowing for oral administration, and a prolonged half-life of 12-24 hours, allowing twice daily administration (ibid). There is a general reluctance to use diazepam for critically ill patients because of its long elimination and concerns about excessive and prolonged sedation. However, similar to methadone, diazepam’s long acting active metabolites theoretically should result in small changes in serum drug concentrations and may decrease fluctuations in sedation state and therefore be a more appropriate agent for long term sedated patients [39].

The formal acknowledgement of a Sedation Weaning phase with a dedicated assessment tool and tapering regime was new practice for the study units. No validated opioid or benzodiazepine weaning schedule was found however a consensus of opinion across the literature supports daily reduction of 5% to 10% or an initial reduction of 20% to 40% and

followed by a 10% reduction once or twice daily, depending on patient response [39 48]. The protocol for sedation weaning incorporated into these guidelines approximated these recommendations.

Guideline Implementation

The guidelines encompassed many changes in practice: new assessment scales, standardising of practice, conversion to oral agents, algorithms, and a discreet weaning pathway. In the interest of maximising staff understanding and uptake of the tools, a phased implementation process was adopted with the gradual introduction of each tool into the units, followed by orientation and implementation to the algorithm phases and medication administration. Staff in-services introducing the study and guidelines were held over an initial fortnight with phased introduction and implementation of each assessment tool over the following months. These were further supported by bedside education on tool use and supplemented by information and teaching aids on the units' computer system.

In practice, the PICU team set sedation and analgesia goals as part of the daily patient review and staff at the bedside (usually nurses) used the guidelines to achieve the set goals.

Outcome variables

Data was collected from all eligible patients over 24 months (12 months historical control and 12 months post implementation), plus a break to allow for the implementation period. In addition to the main study outcomes, the pilot study collected outcomes to establish feasibility of the protocol and processes. The main study outcomes measured included total ventilation time (TVT), sedation doses and duration, length of stay in the PICU (LOS), plus quality indicators such as, accidental extubation and readmission rates. It was important to establish that the outcomes were not adversely effected by the guidelines before considering larger and more extensive trial work. Feasibility data outcomes included the success of screening and recruitment strategies; data collection and entry processes; confirmation of Research Nurse time and cost, and produce further estimates of ventilation times and

medication dosing, that can be used to finalise sample size requirements for the larger trial, and inform funding applications for same. Potentially confounding variables collected included patient age, gender, diagnosis, and the Paediatric Index of Mortality (PIM2) as a measure of acuity. Nurses in the study setting routinely collect and record standard demographic and biophysiologic patient measurements on the local computerised information system. The revised paediatric index of mortality (PIM2) is a simple model of mortality in paediatric intensive care based on admission data and uses ten explanatory variables [49]. Post implementation compliance/fidelity was assessed by chart review using an audit tool based the 19 key components of the guidelines. Adherence to 75% of the key components overall and then within each phase was nominally chosen as the minimum acceptable value for fidelity at this stage. However, the results whatever they were would inform any future implementation processes and trial work. Nursing staff perceptions of the guidelines were ascertained through administration of a researcher developed survey with questions on ease of use, impact on practice, perceived benefit, facilitation of team management, and promotion of nurse autonomy at bedside. Staff members were also given the opportunity to comment on strengths and limitations of the guidelines.

Statistical analysis

Data were analysed using PASW 18.0 (SPSS Inc.). Descriptive statistics were used for demographic data. Continuous values reported were medians and ranges due to the large spread of the data. Categorical variables were reported as counts and percentages. Non parametric Mann Whitney or Cross tabulation and Pearson's Chi Square were performed to compare groups. The probability of remaining ventilated between groups was analysed using survival analysis. Adherence to guidelines was reported in counts and percentages. The influence of diagnostic group on guideline adherence was analysed using Pearson's Correlation and comparison of means using student's T-test. Survey responses were reported in counts and percentages as well as significant themes derived from qualitative data.

Results

During the two study periods (12 months each) 173 and 235 patients were ventilated in the respective pre and post guideline implementation periods. After screening for eligibility 75 and 70 patients were enrolled into the pre and post groups. Seven patients were lost to the study in the posttest group because of deviation from research protocol (n=5), one group of parents did not consent to use of the drugs, and one was transferred to another hospital. Ultimately there were 75 in the control group and 63 in the post implementation group. Data were analysed on a *per protocol* basis. Figure 1 demonstrates the sampling framework and exclusion criteria.

INSERT FIGURE 1

Table 2 shows the main characteristics measured for each sample. Both groups were comparable with no significant differences between age, weight, sex, or reason for admission. There were also no differences identified between the TVT and LOS for each group. There were no incidents of accidental extubation or readmission within 48 hours for subjects in either group for the study.

Table 3 shows the different drug characteristics between groups, demonstrating a greater variance in drug usage. The decrease of 19 hours in the median infusion time of Morphine between groups approached significance (87hrs vs 68 hrs, *p=0.059*). There were changes in the median minimum and maximum Morphine doses, though not significantly. A reduction of 11 hours was identified with median infusion of Midazolam between groups, however this difference was not significant. Significant changes in the median minimum and maximum doses of Midazolam were observed (MIN 10mcg/kg/hr vs 17 mcg/kg/hr, *p <0.001* and MAX 120mcg/kg/hr vs 180mcg/kg/hr, *p<0.001*).

	Pre n=75	*Post n=63*	*Statistic*
Age (yrs) Median (IQR)	2.08(5.6)	1.75(4.5)	NS Mann Whitney
Weight (kgs) Median (IQR)	11.5(15.62)	12(11)	NS Mann Whitney
Sex No (%)	Male 45(60%)	Male 38(60%)	NS Chi square
Primary Diagnosis No (%)	Resp 29(39%)	Resp 21(33%)	NS Chi square
PIM Median (IQR)	5.00 (9)	5.20 (5.3)	NS Mann Whitney
TVT(days) Median (IQR)	4.02(5.36)	3.12(7.68)	NS Mann Whitney
LOS (days) Median (IQR)	6.3(6.76)	5.8(7.90)	NS Mann Whitney

NS = not statistically significant i.e. p≥0.05

Table 2: Baseline characteristics in the study groups

	Pre n=75 *Median (IQR)*	***Post n=63*** *Median (IQR)*	*Difference and Statistic*
Morphine			
Infusion duration (hrs)	87 (136.5)	68 (78)	-19 hrs *p=0.059*
Min dose (mcg/kg/hr)	10 (11)	17 (10)	+7mcg/kg/hr NS
Max dose (mcg/kg/hr)	120 (102.25)	97.5 (52.75)	-22.5 mcg/kg/hr NS
Midazolam			
Infusion duration (hrs)	71 (154)	60 (90)	-11 hrs NS
Min dose (mcg/kg/hr)	10 (12)	24 (20)	+14 mcg/kg/hr *p<0.001*
Max dose (mcg/kg/hr)	120 (101.75)	180 (143.25)	+60 mcg/kg/hr *p<0.001*

NS = not statistically significant i.e. p≥0.05

Table 3: Outcome variable comparison between study groups

Applying the Kaplan-Meier curve of risk to the probability of remaining ventilated to each group demonstrated that posttest group did not have an increased risk of remaining

ventilated (see Figure 2). The probability of remaining ventilated was reduced in the posttest group (by just less than a day at 21 hours); however this was not statistically significant.

INSERT FIGURE 2

Other observed changes in practice were the greater use of adjunctive and alternative medication, in particular methadone. Results showed that prior to the guideline implementation there was limited use of alternative medications (1-2 alternative medications or even none). Post guideline implementation the numbers of alternative medications used increased. More detailed analysis revealed a significant difference with the use of Methadone pre 3% - post 33% *p<0.001;* Diazepam pre 5% - post 25%, *p=0.001;* Chloral Hydrate pre 32% - post 58% *p=0.002;* Propofol pre 60% - Post 20% *p<0.001;* and Neuromuscular blockade agents pre 60% - post 47.6% *NS.*

Implementation fidelity (Chart Audit)

Sixty-three charts from the post implementation period were reviewed to identify the level of staff adherence to the 19 key components of the guidelines and quantify the level of assessment and scoring. Overall adoption was achieved in 23 (36%) of the charts audited. Separate analysis within each of the phases demonstrated that adoption was achieved in 30 (47.6%) in the acute phase, 23 (36.5%) in plateau, and 25 (39.7%) in the weaning phase. Pain and sedation scores were assessed and documented in 95% (n=60) of charts in the acute and plateau phases, and 85% (n=54) of charts in the weaning phase. The withdrawal score was assessed and documented appropriately in 75% (n=47) of charts.

Staff survey

The response rate was 49% (n=54). Participants' responses were divided into four categories: awareness/use, strengths, limitations and suggestions for improvement. Fifty-two (96%) staff regularly referred to the guideline to assist with decision making and to provide

prompts and cues. There appeared to be some confusion as to who was primarily responsible for the initiation of the guidelines, with 12(23%) suggesting is was the consultants' responsibility and 32(60%) stating it was the bedside nurse. Table 4 outlines further responses.

Questions	***Yes Response n=54***
The sedation guidelines and flowchart are easy to follow	58.5%
The flowchart facilitates the sedation management process	87%
Patients benefit from having a constructive escalation program	96.3%
Patients benefit from having a constructive titration program	94.3%
Patients benefit from having a constructive weaning program	96.2%
A multidisciplinary approach enhances sedation management	96.3%
The guidelines give me more autonomy in managing sedation	68.5%
The guidelines improve overall sedation management	88.5%

Table 4: Staff perceptions of sedation guidelines in practice

Perceived strengths of the tool included the structured nature of the guidelines, promotion of consistency in practice and the resulting increased awareness regarding sedation management. Conversely perceived limitations included the perceived complexity of algorithm, confusion with delineation and movement between phases, and the lack of accommodation of increased drug tolerance with long term patients. Staff suggested simplifying the algorithm and using larger print, incorporating recommendations for short term patients and providing clinical example as guides. . Table 5 provides a sample of staff comments on perceived strengths and weaknesses of the guidelines Overall four major themes were expressed by study participants (see table 5): (1) a knowledge deficit about some aspects of the guidelines, (2) high value placed on individualised patient care, (3) perceived ineffectiveness of the guidelines for some patients, and (4) disagreement between doctors and nurses on responsibilities.

Strengths
▪ The bedside nurse 'knows' the patient and their requirements, can initiate changes, use objective data on the screen, can see changes and ask for review if needed. ▪ It is a clinical tool to justify an increase or decrease in sedation. Allows for uniform/consistent decision making. ▪ Empowers and rationalises nursing changes in sedation. ▪ Everyone using the same guide should translate to more consistent care. There is more autonomy for nurses, particularly with less experienced registrars. It potentially irons out variations in individual consultant preferences. ▪ It has increased the awareness amongst staff and prompts discussion. ▪ It places importance on sedation and assists nurses to provide better sedation. Patients more comfortable equals parents more comfortable.
Limitations
▪ Can be complicated because of the amount of detail. ▪ Needs definitions and differential diagnoses for each of the phases. ▪ Not all patients fit the guidelines or respond as predicted. ▪ Requires full concentration with attention to detail and practice to become familiar. ▪ Lack of medical leadership/ownership shared. ▪ Difficult to continue in ward, particularly with weaning. ▪ Have trouble with some long term patients following the guidelines and keeping them comfortable.

Table 5: Staff perceptions of strengths and limitations of sedation guidelines.

Discussion

This pragmatic pilot study demonstrated the use of guideline directed sedation and analgesia management was not associated with increased ventilation times or PICU length of stay. The results of the study also showed that the guidelines were generally feasible and acceptable in the clinical practice with predominantly positive feedback from nursing staff using them. Full adoption of all aspects of guidelines was not realised but results demonstrated improved levels of patient assessment, increased use of enteral agents (in line with guideline recommendations)..

The observed increases in median minimum and maximum doses of Morphine and Midazolam do not appear to be associated with an increase in patient TVT or LOS, and in

fact the duration of each infusion was reduced,. Similar changes in medication administration have been observed in other PICU guideline studies [16-20].

The results of Kaplan-Meier Risk analysis indicate that there was potentially a reduced risk of remaining ventilated in the post-test group.. However, a median difference of 21 hours between groups may be viewed as 'clinically significant' as this time difference in the clinical setting could translate to earlier extubation and/or discharge. Larger, randomised trial studies are warranted to allow firm conclusions to be made.

Only a small proportion of participants were ultimately eligible for the study (43% and 31% respectively), which has implications for the projected timeline, research assistant time and costs and data collection for a larger multi site trial. The results also revealed the huge spread of the clinical data and the challenge this posed for researchers. Follow on studies would possibly need to consider subcategories of patients i.e. short, medium and long term ventilated and analysing within these categories.

The guidelines and implementation process in this study also appear to have increased awareness and usage of alternative medications to complement or replace the Morphine/Midazolam. This was particularly evident with the use of Methadone and Diazepam. Use of Methadone rose from 3% pre test to 33% post test. Use of Diazepam rose for 5% pre test to 25% post test. One of the key recommendations to emerge from the literature and therefore included in the guidelines was the transition from continuous intravenous analgesia and sedation to regular oral agents. Prolonged administration of opioids and benzodiazpines may result in the development of drug tolerance and then withdrawal syndrome if these agents are abruptly discontinued [9 38 50 51]. Research has shown that this can be prevented by slowly tapering the intravenous administration of the drug or switching from intravenous morphine and midazolam to orally active drugs with a

longer half-life, such as methadone and diazepam [45 47]. In general the increased use of adjunct medication was evidence of the clinician use of guideline recommendations.

Sedation, Pain and Withdrawal scores were all captured but difficult to summarize meaningfully as a research variable. We recommended that a useful variable for follow in studies be to calculate the percentage of time each patient spent in a designated 'zone' and determining appropriateness and success /failure of management accordingly.

The audit of implementation fidelity demonstrated that the assessment and documentation of patient's pain and sedation was well recorded, reflecting sound staff understanding and uptake of the new assessment tools. The adoption score for the withdrawal phase was the lowest of the three phases, which may have resulted from less familiarity and knowledge with the tool and phase. This is consistent with findings were found in a review of similar studies [52]. Suggested reasons for non-adherence included complexity of guideline or algorithm, staff not valuing or understanding goal of guideline, perceived redundancy of guideline if staff already competent practitioners in this area (ibid). Potential solutions to these issue included ongoing staff education and timely feedback related to the guideline to continuously reinforce importance, ease of use, and troubleshoot issues[53]. In addition to surveying staff opinion, it is also important to conduct periodic chart audits to quantify guideline fidelity. This will help minimise self-report bias as was somewhat reflected in this study[54]. Staff perceptions of guideline principles and use were positive although level of adherence variable. So the full impact of the guidelines were not realised.

In conjunction with the audit, a survey of nursing staff perceptions and attitudes were undertaken to establish if these influenced adoption of the guidelines. In line with other similar studies, nurses were largely positive and constructive in their feedback[18 55 56]. All feedback has been utilised to improve the guidelines. Engaging staff and providing feedback during the process of procedural change is a vital step in optimising follow trial success and

ultimately translation to practice. Follow on trials should also build in mechanisms to capture multidisciplinary staff experience and feedback.

The importance of the findings of this study are that they indicate that collaborative guidelines can be used to manage the PICU patient's comfort and pain without compromising quality of care (TVT, LOS, quality indicators). The results are similar to those in the adult population where guideline or protocol driven sedation has been linked to a reduction in duration of continuous intravenous sedation, ventilation time and associated health care costs [57-61]. Evaluation of feasibility outcomes has aided in development a realistic plan regarding participant recruitment, staff education to optimise guideline fidelity, safety of guidelines in clinical practice and collection of key outcome variables.

Implications & Recommendations

No definitive causal effect can be attributed to the guidelines on outcomes due to the pre post study design and small sample size. Full adoption of all phases and tools in the guidelines was not realised and this has implications for ongoing implementation and larger trial work. Additionally the small response rate and selective population for the survey may introduce some bias in the current understanding of staff acceptance of the guidelines. A more inclusive (medical and nursing) survey population is recommended for follow research. Conducting the study in two units assists with the generalisability of the study and its results. Some specifics of the guidelines and algorithm, however, might need modification to reflect local practice. For example, use of different drugs (fentanyl instead of morphine) and different patient populations (post cardiothoracic surgery).

The study results are most useful in informing the structure and outcome measures for a follow on clinical trial in this area.

Results from the study, audit and survey have informed changes and modifications to optimise staff understanding and use of sedation guidelines in practice. Weaning from

sedation agents and the concept of withdrawal appear to be areas of practice that need more attention. The researchers went on to trial and evaluate a revised withdrawal assessment tool and a study comparing the outcomes of Dexmedetomidine versus Midazolam is about to commence. The study units plan to continue to use the guidelines and tools in their modified form pending the results of larger trial work recently completed in the USA. The modern ICU is an important focus for quality improvement efforts. Guidelines cannot automatically guarantee improved quality of care; however, they do direct the clinician in the pursuit of this objective particularly when supported by high level evidence.

Contributorship statement:

All three authors, Samantha Keogh, Debbie Long and Desley Horn meet the key three ICMJE guidelines for authorship with each having made (a) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content; and (c) final approval of the version to be published.

Competing interests

None of the authors have any competing interest or financial disclosure related to this study to declare.

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Data sharing statement

A copy of the guidelines can made available by emailing Debbie.Long2@health.qld.gov.au.

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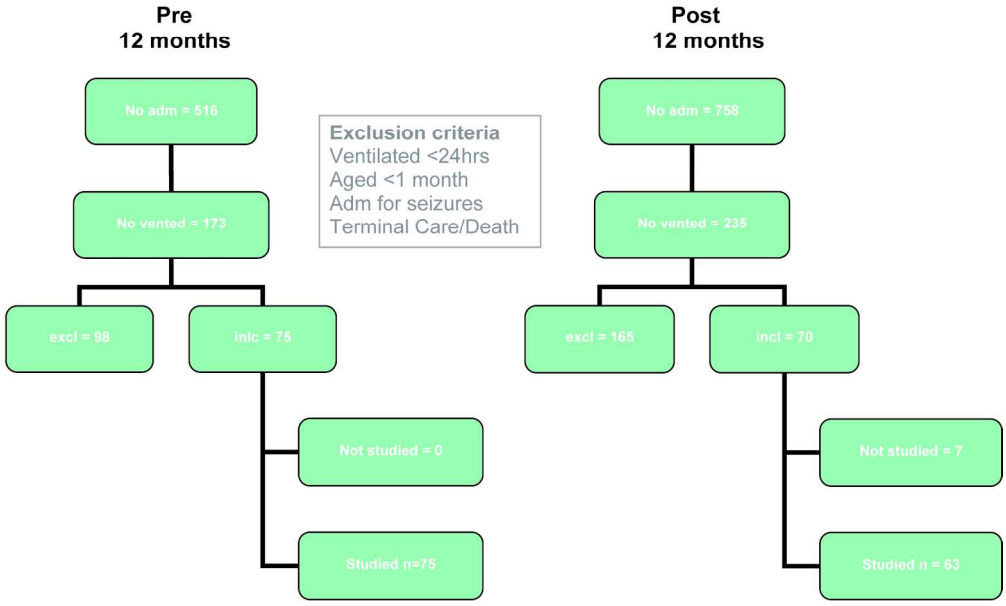
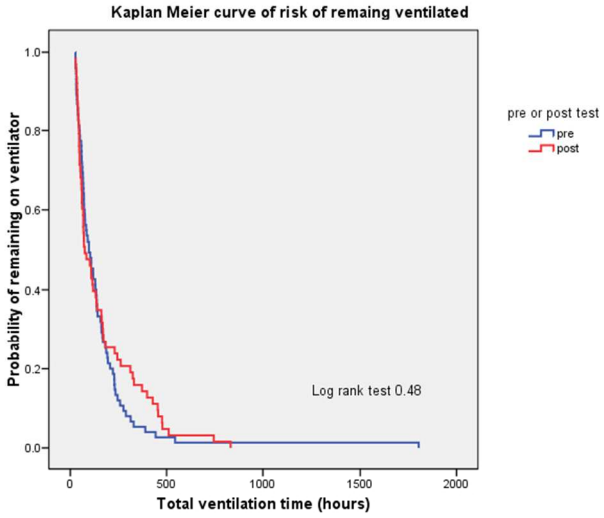
Figure 1: Sample framework



172x113mm (300 x 300 DPI)

Figure 2: Kaplan-Meier Curve of risk of remaining ventilated between groups



209x297mm (98 x 98 DPI)

GUIDELINES FOR THE ADMINISTRATION OF SEDATION AND ANALGESIA IN MECHANICALLY VENTILATED CHILDREN

PURPOSE:
To outline the management of sedation and analgesia in critically ill children receiving mechanical ventilation.

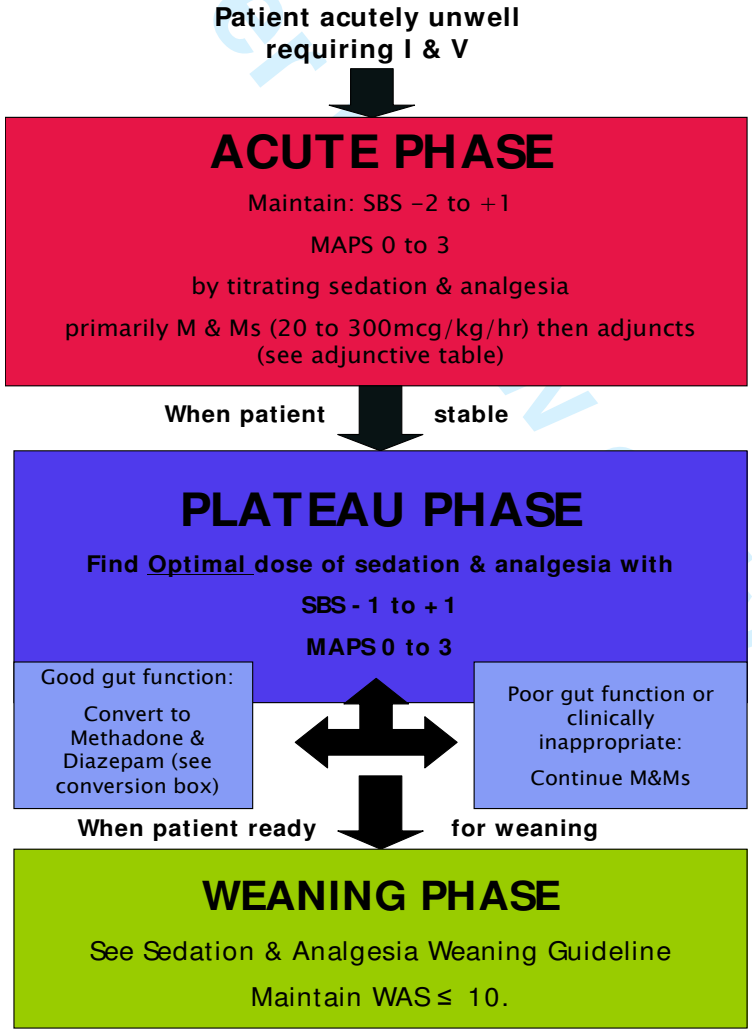
BACKGROUND / SUPPORTIVE DATA:
Sedation and analgesia are necessary components of the care of all critically ill children, especially those requiring mechanical ventilation. The main indications for the use of sedation and analgesia include: to reduce pain and discomfort, to reduce anxiety and agitation, to induce amnesia, to facilitate mechanical ventilation, to prevent the displacement of endotracheal tubes, and to decrease cellular metabolism. The consequences of prolonged use of sedative and analgesic agents in the PICU patient include central nervous system activation, gastrointestinal disturbances, and sympathetic hyperactivity. These signs and symptoms have been related to tolerance and withdrawal phenomena and hold implications for the patient's physical and psychological well being as well as health care costs.

Tolerance is one of the major reported adverse effects associated with continuous benzodiazepine infusions. Tolerance may be defined as a decrease in the effectiveness of a drug after prolonged use or as the requirement of larger doses to achieve the same effect. This phenomenon is due to an adaptation of neuronal cells and not a change of metabolism of the drug. One method of addressing this adverse effect, drug tolerance, is to recognise its occurrence and introduce alternative sedation agents titrated to an accepted sedation level.

A second adverse effect of the prolonged use of analgesic and sedation agents is withdrawal or abstinence syndrome. In paediatric patients, withdrawal syndrome is due to the development of tolerance to sedation and analgesic drugs not dependence or addiction. Studies have shown a strong positive correlation between large total doses of midazolam and the occurrence of withdrawal symptoms. Local, national and international audits have all shown that drug tapering is conducted in very few patients and that most patients have their sedation and analgesic agents abruptly discontinued. Thus, the incidence of withdrawal symptoms may be related to the infrequent tapering of sedation and analgesic agents.

There exists a plethora of literature discussing the adverse effects of sedation and analgesia in the critical care environment, particularly its prolonged use. There appears to be a consensus about the need and benefits of a systematic and coordinated approach to sedation administration, tapering and titration in the PICU.

SUMMARY OF SEDATION ALGORITHM:



EVIDENTIARY TABLE:

Strategy	Evidence
Use of protocol	The use of protocol directed sedation can reduce the duration of mechanical ventilation, ICU and hospital stay and can result in safe, cost-effective improvements.[1-5]
SBS – Sedation Scale	Reliable and valid scale for use in paediatric critical care.[6-8]
PICU MAPS – Pain Scale	Reliable and valid scale for use in paediatric critical care, particularly pre-verbal children.[9-12]
Withdrawal Assessment Scale	Combination of validated tool and Great Ormond Street Hospital protocol[13-18]
Accumulative dose	Up to 300 mcg/kg/hr for Midazolam
Weaning timeframes	[13, 19]
Mandatory review	[20]
Conversion to oral drugs	Diazepam, Methadone [24-26]

SUGGESTED PHARMACOLOGICAL TREATMENT OF PROCEDURAL PAIN AND DISCOMFORT:

Drug Group	Drug	Indications	Evidence
Topical Local Anaesthetic	Angel Cream EMLA	PIV/IAL insertion Venepuncture Arterial Stab Portacath access Lumbar puncture* CVL/ICC insertion*	[1-5]
	Lignocaine 2% & Chlorhexidine 0.05%	IDC insertion	[6, 7]
	Lignocaine 4%	Bronchoscopy*	[8, 9]
Sub-cutaneous injection	Lignocaine 1%	ICC/CVL insertion*	[2]
Disassociative Agent	Ketamine	CVL/ICC insertion Gastroenterology procedure Bronchoscopy Bone marrow aspiration Wound management procedure	[10, 11]
Short acting anaesthetic agent	Propofol	CVL/ICC insertion Gastroenterology procedure Bronchoscopy Bone marrow aspiration	[10, 12]
Short acting sedative & analgesic agent	Morphine & Midazolam	ETT Suctioning Movement/Position change	[30]

* used in conjunction with other drugs

SUGGESTED NON-PHARMACOLOGICAL MEASURES FOR OPTIMISING PATIENT COMFORT

Treatment	Evidence
Positioning & body support	[13-16]
Reassurance by staff and/or parents	[14]
Minimise discomfort of invasive devices (e.g. ETT, CVLs, and drainage tubes).	[14]
Optimise hydration, nutrition, essential cares (e.g. mouth, eye).	[17-19]
Massage, or rocking	[20, 21]
Swaddling	[22-24]
Non-nutritive sucking	[25-27]
Decrease external stimuli (noise, light, movement or handling)	[15, 28, 29]
Music therapy	[20]

SUGGESTED ADJUNCTIVE PHARMACOLOGICAL THERAPIES FOR MAXIMISING PATIENT COMFORT

Drug	Approach	Evidence
Propofol	2.5-3.5mg/kg stat then 7.5-15mg/kg/hr[30] ; 4-6mg/kg/hr[31]	[30-34]
Morphine	20mcg/kg prn	[30]
Midazolam	20mcg/kg prn	[30]
Ketamine	1mg/kg/hr	[30, 32, 33, 35]
Chloral Hydrate	25mg/kg q6h[36] maximum 5g	[35, 36]
Fentanyl	If allergic or renal failure 5-10mcg/kg/hrl	[30, 34, 35]
Promethazine	Oral 0.5mg/kg q6h Maximum 1mg/kg	[37]
Chlorpromazine	0.25-1mg/kg/q6-8h	
Clonidine	3-5mcg/kg q8h	[30, 35, 36, 38]
Haloperidol	0.1mg/kg- 0.1mg/kg q12h	[39]
Phenobarb	5mg/kg/day	[36]
Paracetamol	90mg/kg/24hrs- accumulation in hepatotoxic in pts with impaired LF-	[30]
Codeine	Max 1mg/kg/dose	[30]
Ibuprofen	10mg/kg q6h Precautions- asthma, renal impairment, under 6mths	[30]

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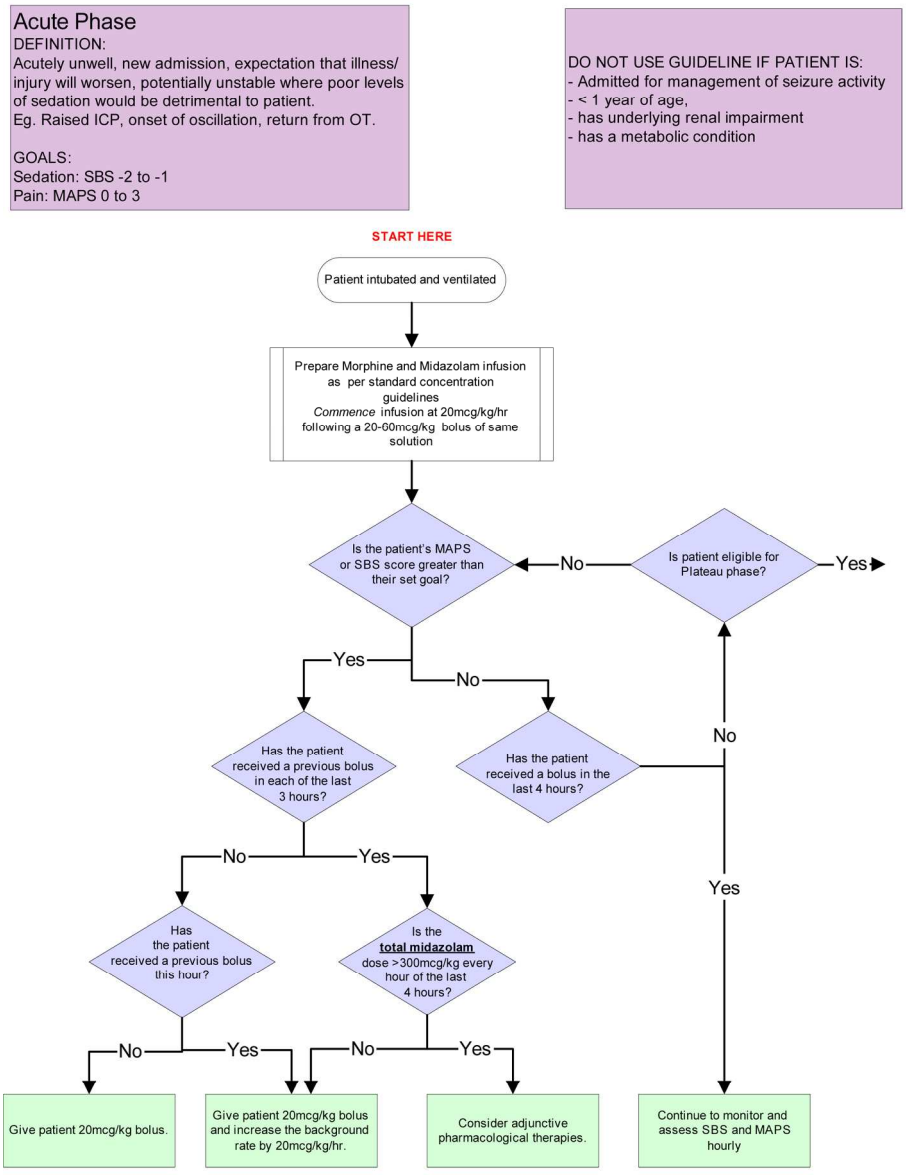

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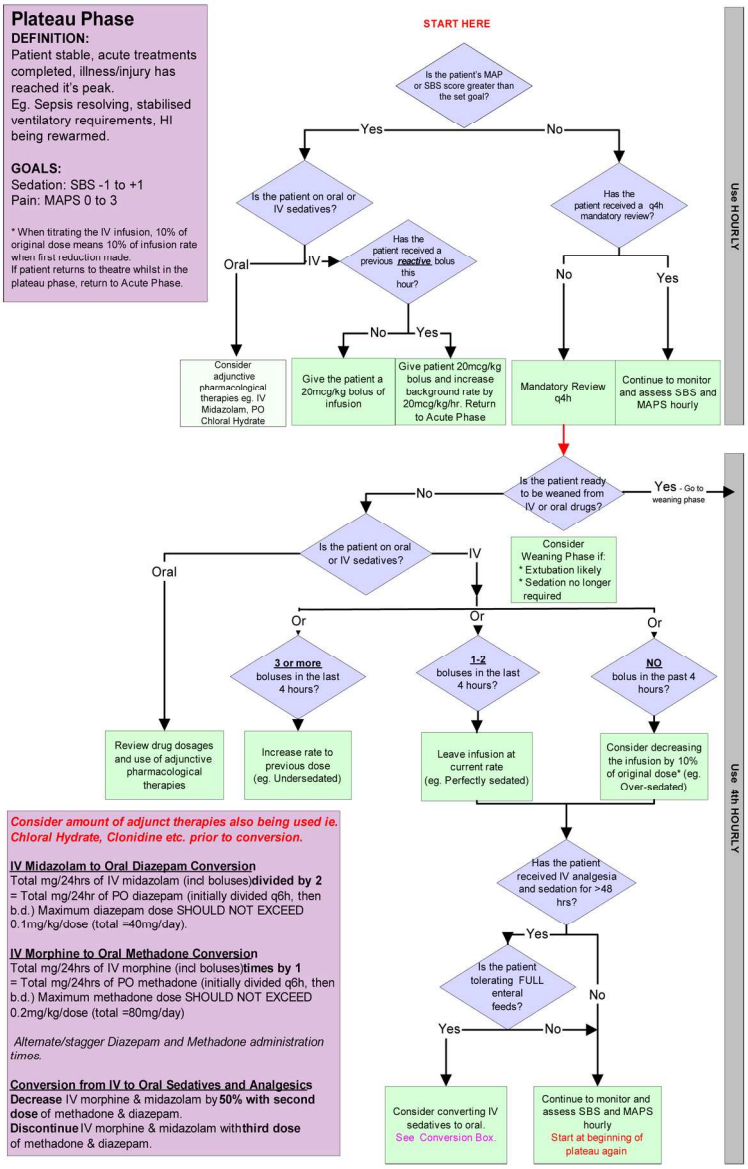

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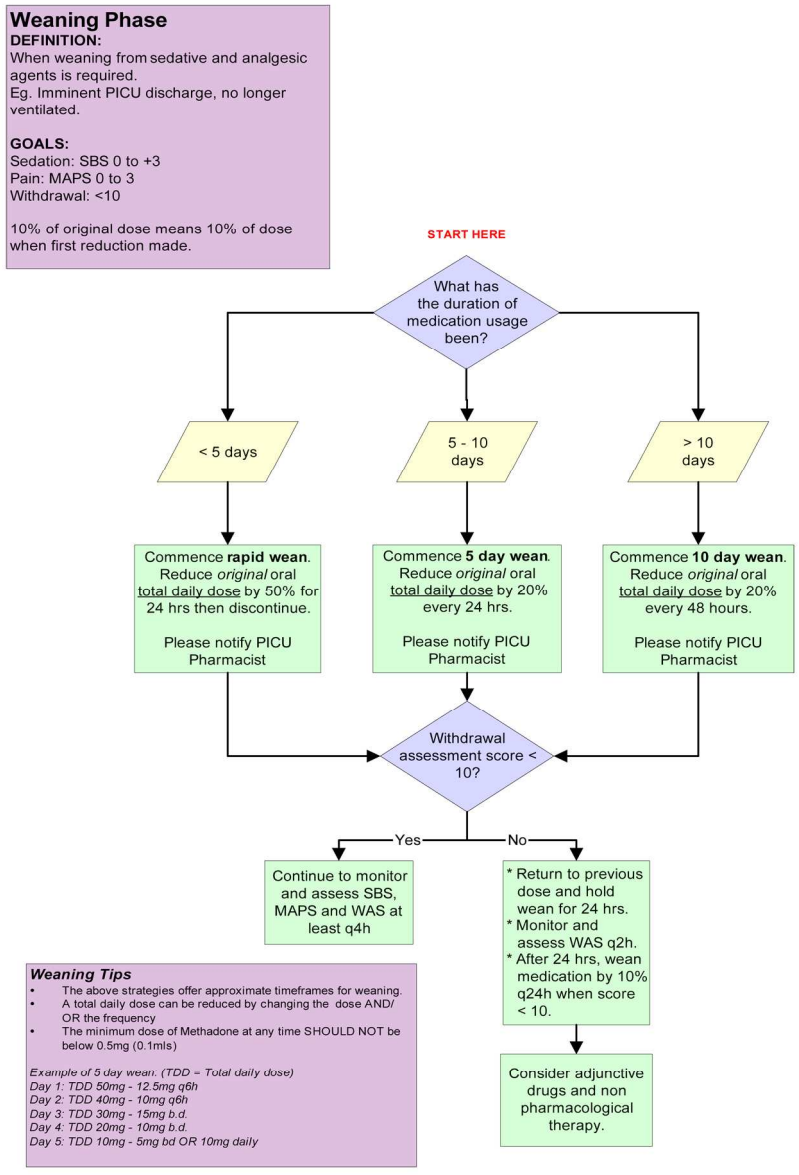

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