Infection Was Associated With Intensive Care Unit Pediatric Delirium in Children Younger Than 2 Years Old: A Single-Center Observational Study

Xiaohua Ge (gexiaohua@xinhuamed.com.cn)
School of Nursing, Naval Medical University, Shanghai
Wanrui Wei
Department of Nursing, Xin-Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai
Qingru Zheng
School of Nursing, Shanghai Jiao Tong University, Shanghai
Lili Xu
Pediatric Intensive Care Unit, Xin-Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai
Yaqin Hu
Pediatric Intensive Care Unit, Xin-Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai
Changrong Yuan
School of Nursing, Naval Medical University, Shanghai

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Infection was Associated with Intensive Care Unit Pediatric Delirium in Children Younger than 2 Years Old: a Single-center Observational Study

Xiaohua Ge, RN, MSN [1,2*†]; Wanrui Wei, RN, MSN [2,3†]; Qingru Zheng, RN, BSNurs [3]; Lili Xu, RN [4]; Yaqin Hu, RN [4]; Changrong Yuan, PhD, RN, FAAN [1,5*]

[1] School of Nursing, Naval Medical University, Shanghai, China

[2] Department of Nursing, Xin-Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

[3] School of Nursing, Shanghai Jiao Tong University, Shanghai, China

[4] Pediatric Intensive Care Unit, Xin-Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

[5] School of Nursing, Fudan University, Shanghai, China

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*Correspondence: gexiaohua@xinhuamed.com.cn ; yuancr@fudan.edu.cn

†Xiaohua Ge and Wanrui Wei contributed equally.

Key Words: pediatric; children; critical care; delirium; infection; hypoxia

Abstract

Objective: The primary objective of this study was to investigate the prevalence of intensive care unit (ICU) pediatric delirium in Shanghai, China. Secondary objectives were to determine the association of hypoxia and infection with ICU pediatric delirium, and the impact between different age.

Design: Prospective single-center observational study.

Setting: Two pediatric intensive care unit (PICU) within a tertiary-A general hospital.

Patients: Patients age between 1 month to 7 years in PICU who stayed at least 1 day were included. Convenance sampling was used.

Interventions: None.

Measurements and Main Results: Pediatric patients (n=639) were screened twice a day for the prevalence of ICU pediatric delirium by Cornell Assessment of Pediatric Delirium, 300 (46.95%) of them had infection and 213 (33.33%) had hypoxia in PICU. Children who suffered hypoxia remained more than three times likely to be delirious during their hospitalization compared with children who were not hypoxia, after controlling other covariates, the odds of pediatric delirium for subjects with hypoxia was 3.26 times (95% CI, 1.98-5.38) the odds without hypoxia. Also, the odds of pediatric delirium for subjects with infection was 2.55 times (95% CI, 1.58-4.11) the odds without infection adjusting for other covariates. After subgrouping by age, the occurrence of ICU pediatric delirium with infection for children younger than two years old was 5.37 times

(95% CI, 3.09-9.33) compared with patients who were never infection, while that for the children equal to or older than two years old was no statistically significant relationship.

Conclusions: The prevalence of ICU pediatric delirium was 31.30%, while there is an independent association of infection and hypoxia with ICU pediatric delirium. Furthermore, children younger than two years old took more risks on pediatric delirium when they were infected in this study, while there was no relationship between infection and pediatric delirium who aged 2 years or older.

Introduction

Delirium is the general term of all acute or subacute generalized cognitive impairments (1). Pediatric delirium is usually characterized by changes in psychomotor activity, including delayed response, sustained and agitated physical activity, and crying that is difficult to soothe or abnormal. ICU pediatric delirium not only leads to increased hospital mortality, prolonged mechanical ventilation, and length of hospital stay; but brings a series of short-term and long-term hazards to pediatric patients as well (2–4); meanwhile, pediatric delirium is associated with a substantial increase in pediatric intensive care unit (PICU) medical expenditures (5). The longer the duration of ICU pediatric delirium, the more harmful it is (6).

The prevalence of ICU pediatric delirium ranges from 12% to 47% (7–15).

Children at young age (<2 years), disease severity, infectious diseases, inflammation, mechanical ventilation, physical restraint, vasopressors, and antiepileptic drugs are proved to be risk factors for ICU pediatric delirium (10, 16, 17). Preventions on pediatric delirium could be designed considering risk factors, thus, it's vital to make sure the independent risk factors of pediatric delirium. Maldonado (18, 19) summarized that at least six pathophysiology and seven neuropathogenesis theories develop delirium, and their combination of several or all helps to explain how delirium occurs and develops in hospitalized patients, among them, hypoxia and infection are routine collected indicators which are more objective and relatively easier controlled in PICU. They are associated with a high occurrence of delirium in the adult population group.

Engel and Romano proposed Oxidative Stress Hypothesis (OSH) which demonstrates many physiologic processes such as hypoxia and infections may finally contribute to delirium cognitive and behavioral symptoms (20). In addition, infection may introduce triggering factors giving rise to the inflammatory cascade activation including hypoxia, blood transfusions, elevated hormone levels and so on. Furthermore, systemic inflammation which may be caused by injury (including surgery) or infection has long been considered a triggering cause of delirium (19).

At the same time, the complex association between hypoxia, infection and ICU pediatric delirium might provide an insight into the possible therapeutic measures in ICU. What' s more, the prevalence of ICU pediatric delirium and

the association of hypoxia and infection with ICU pediatric delirium have remained unclear in China. Therefore, we aimed to investigate the prevalence of delirium in a Chinese PICU as well as the impact of hypoxia and infection.

Materials and Methods

Study Design, Setting, and Patients

This prospective observational study was conducted in 2 PICU at Xinhua Hospital affiliated to Shanghai Jiao Tong University, which is a tertiary-A general hospital in Shanghai, China. Pediatric patients admitted to the unit from December 1, 2018 to August 31, 2019, were included. Convenient sampling was used. The inclusion criteria were as follows: ① Age was between 1 month and 8 years; ② ICU check - in time was more than 24 hours; ③ Informed consent was obtained from a parent/guardian. The exclusion criteria were as follows: ① Children were with delirium existed before admission; ② After being admitted, they were in a coma or deep sedation with Richmond agitation sedation scale (RASS) <-3; ③ Patients who continued to be administered antipsychotic drugs; ④ Patients were after neurosurgery or neurological surgery; ⑤ Missed or incomplete delirium score; ⑥ Hearing or visual impairment; ⑦ Non-Chinese or Non-English language users. The endpoint was either a discharge of the patient from the ICU or death. The protocol was approved by Xinhua Hospital Ethics Committee Affiliated to Shanghai Jiao Tong University School of Medicine (Approved No.

of ethic committee: XHEC-C-2018-097). The ICU responsible nurses explained this study to the children' guardian when nurses making entrance education to them, and the guardians voluntarily signed informed consent forms. The study was registered in the Chinese Clinical Trial Registry, which was part of the International Clinical Trials Registry Platform of the World Health Organization (Registration number: ChiCTR1800019825 http://www.chictr.org.cn/showproj.aspx?proj=33238).

Outcome Measure and Data Collection

The primary outcome is ICU pediatric delirium, each patient was screened for delirium twice daily by the researcher using the Cornell Assessment of Pediatric Delirium (CAPD) (8, 10, 15, 21, 22). The RASS> -3 and CAPD score> 9 were considered pediatric delirium positive and a patient who has been screened for pediatric delirium positive at least once during intensive care is defined as ICU pediatric delirium. What's more, the data collectors were the researcher herself and ICU nurses, and the researcher has been authorized by the scale inventor and the translator for the Chinese version. The pilot experiment (n = 20) in this study measured Cronbach 's α of CAPD as 0.97, and the scale reliability was good. Severity of illness was measured by Pediatric Risk of Mortality score IV (PRISM IV) (23) within 4 hours from every patient admitted in the PICU. The higher the score, the more critical the patients are. Demographic and clinical indicators were recorded from Hospital

Information System, while laboratory results, treatment and nursing data were recorded from Hospital Information System and ICU nursing record every study day. When the patient's white blood count, neutrophil ratio, and daily maximum body temperature were out of normal range, the patient was judged to be infected; when the patient's arterial blood oxygen pressure (PaO_2) was less than 80mmHg, the patient was judged to be hypoxia.

Statistical Analysis

SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. For normal distribution data, the (mean ± standard deviation) was used for description; for non-normal distribution data, the median and interquartile range (IQR) were used for description, and for categorical data, frequency and percentage were used for description; measurement data comparison between groups were all compared by univariate logistic analysis. Multivariable Logistic regression following univariate logistic analysis was performed. The multivariable logistic-forward-maximum likelihood ratio (LR) test conditional method was used for regression analysis. The significant level of the deleted variables was 0.05, and the significant level of the excluded variables was 0.10. All hypothesis testing was two-tailed, and statistical significance was assessed at the 0.05 level.

Results

During the study period, 639 patients in the PICU met the criteria were finally admitted in this study and the prevalence of ICU pediatric delirium was 31.30%. The age range is 1-84 months, and the average age is (19.51 ± 23.58) months. Among 3703 study days, delirium occurred in 581 (15.69%) study days. Among 200 children with ICU delirium, the first onset of ICU pediatric delirium occurred within the first seven admission days to PICU. Among them, 176 cases (88%) of delirium occurred in the first three admission days to PICU, 148 cases (74%) of delirium occurred for the first time within 48 hours of admission to the PICU, 95 cases (47.5%) of delirium occurred for the first time within 24 hours of admission of PICU; 107 cases (53.5%) with the total number of ICU pediatric delirium duration days was one day. The average was 1.79 (SD = 1.49) days of duration days of ICU pediatric delirium, the median was one day, and the longest duration was nine days, while the shortest was one day. 36% of patient days with delirium were hyperactive, 41% of patient days with delirium were hypoactive, and 23% of patient days with delirium were mixed-type.

Demographics, laboratory results, and clinical characteristics information are shown in Table 1. Pediatric delirium occurred in 200 of 639 patients (31.3%) after PICU admission. Of these, a total of 300 (46.95%) patients had infection and 213 (33.33%) patients had hypoxia, and 160 (25.04%) had both of them while 286 (44.76%) had neither. In the group of infected patients, a total of 160 (53.33% experienced pediatric delirium in patients who had infection vs. 11.8%

experienced pediatric delirium in patients who were never infected) experienced pediatric delirium, while 122 hypoxia patients (57.28% experienced pediatric delirium in patients who had infection vs. 18.31% experienced pediatric delirium in patients who were never hypoxia) experienced pediatric delirium ($P < 0.001$).

As shown in Table 2, in this entire prospective cohort, hypoxia was associated with pediatric delirium in univariate analysis (odd ratio [OR], 5.98 for delirium in patients who were hypoxia when compared with patients who were never hypoxia; 95% CI, 4.15-8.63); infection was associated with pediatric delirium in univariate analysis (odd ratio [OR], 8.54 for delirium in patients who were hypoxia when compared with patients who were never hypoxia; 95% CI, 5.72-12.75). There is no statistical relationship significantly between children who suffered hypoxia and infection simultaneously and pediatric delirium.

Children who suffered hypoxia remained more than three times likely to be delirious during their accommodation compared with children who were never hypoxia, after controlling other covariates (odd ratio [OR], 3.26; 95% CI, 1.98-5.38). Also, the odds of pediatric delirium for subjects with infection was 2.55 times (95% CI, 1.58-4.11) the odds without infection adjusting for other covariates.

Multivariable logistic regression model for association of hypoxia and infection with ICU pediatric delirium based on age is shown in Table 3. We divided data into subgroups by age. After adjusting, the occurrence of ICU pediatric delirium

with infection for children younger than two years old was 5.37 times (95% CI, 3.09-9.33) compared with patients who were never infection, while that for the children aged two years or older was no statistically significant relationship.

Discussion

To our knowledge, this is the first single-center, prospective observational study reported to date investigating the association between hypoxia and infection with the prevalence of ICU pediatric delirium in China. We report a significant association between hypoxia and infection with the occurrence of ICU pediatric delirium.

Although the association about hypoxia with pediatric delirium has not been explored previously in children, studies in adults have reported conflicting effects of hypoxia on the occurrence and development of delirium. Jayaswal has shown hypoxia significantly worsened ICU delirium (24). Similarly, hypoxia was a risk factor contributing to delirium in Palliative Care Unit (25) and one of risk factors for postoperative delirium among geriatric patients postorthopedic surgery (26). However, Lopez (27) have found that hypoxia was not the independent risk factors for postoperative delirium (odd ratio [OR], 1.12; 95% CI, 0.97 - 1.29), while intraoperative hyperoxia cerebral reperfusion was (odd ratio [OR], 1.65; 95% CI, 1.12 - 2.44).

Among critically ill children with infectious or inflammatory diseases, ICU children have the highest prevalence of delirium (10). Otherwise, preoperative

infection is one of the critical predictors of postoperative delirium among the elderly with cognitive deficits (28). In addition, the elderly suffered postoperative pneumonia (odd ratio [OR], 2.97; 95% CI, 1.06- 8.35) or a urinary tract infection (odd ratio [OR], 3.52; 95% CI, 1.72- 7.22) were all risk factors for postoperative delirium (29). However, Dechnik found that there is no association between C-reactive protein or procalcitonin levels and the development of delirium in PICU, while C-reactive protein or procalcitonin are systemic inflammatory markers. At the same time, in this study, in the subgroup analysis, infection was not an independent risk factor for children who aged 2 years or older. This may be due to the higher susceptibility of children younger than 2 years old, and there need more researches in the future to explore the relationship between infection or inflammation and pediatric delirium.

Furthermore, the association between hypoxia and infection are scientifically plausible. More than half of participants experiencing delirium who are adult (≥18 years) medical or surgical ICU patients with respiratory failure, shock, or both had hypoxic, hypoxia and sepsis have well established mechanisms of cellular injury that can affect the brain (30). Whereas intermittent hypoxia is known to cause brain damage (31, 32), Lopez (33) has reported that intraoperative oxidative damage was independently associated with increased postoperative delirium. In addition, among a group of patients undergoing on-pump cardiac surgery, preoperative regional cerebral oxygen saturation

could predict delirium after cardiac surgery, as low baseline cerebral hemoglobin O_2 saturations was associated with increased postoperative delirium (34). What's more, delirium is also regarded as a secondary complication of systemic infection (35) and is thought to be a result of neuroinflammation in a brain with increased release of brain cytokines resulting in direct neuronal damage (18), infection may lead to the inflammation stress, and finally increase the prevalence of delirium.

There are several limitations in this study. Foremost, it is an observational study with convenient sampling and can only suggest an association and not establish causality. Although we reported the relationship between hypoxia and infection and ICU pediatric delirium, we did not collect intraoperative cerebral oxygenation, the degree of hypoxia and infection, therefore, the relationship should be further explored in the future studies. In addition, there are factors that may lead to the occurrence of delirium, such as sleep disturbance and deprivation, parents visiting, or noise and light level, which we did not include in our analysis. Finally, this study was conducted in a single center in Shanghai, thus, the research outcomes may not be widely generalizable. Multi-centered studies are needed to validate the association between hypoxia and infection and ICU pediatric delirium.

Conclusions

In conclusion, this study demonstrated that patients who experienced infection

and hypoxia in ICU carried a high risk for progression to ICU pediatric delirium, and there is an independent association of infection and hypoxia with ICU pediatric delirium. Furthermore, children younger than two years old took more risks on pediatric delirium when they were infected in this study. These notable findings deserve more consideration when it comes to pathophysiology and treatment that will determine its practical and clinical benefit in critical care pediatric patients.

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Author information

School of Nursing, Naval Medical University, Shanghai, China
Xiaohua Ge & Changrong Yuan
Xin-Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China
Xiaohua Ge & Lili Xu & Yaqin Hu
School of Nursing, Shanghai Jiao Tong University, Shanghai, China
Wanrui Wei & Qingru Zheng

School of Nursing, Fudan University, Shanghai, China
Changrong Yuan

Contributions

The study was conceptualized and designed by three authors (Ge X, Wei W&Yuan C). Wei W, Zheng Q, Xu L and Hu Y collected the data; four authors participated in the data analysis (Ge X, Wei W,Zheng Q&Yuan C). Manuscript was written by Ge X, Wei W&Yuan C, All authors read and approved the final manuscript.

Corresponding author

Correspondence to Changrong Yuan and Xiaohua Ge

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine(approval number:XHEC-C-2018–097). All procedures performed in this study was in accordance with the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki declaration and its subsequent amendments or comparable ethical standard. The guardians of enrolled children gave written informed consents to participate this research project.

Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due to the on-going further analysis on other variables with pediatric delirium collected during the study but are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Competing interests

We declare no financial interests or conflicts.

Supplementary Files

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