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国外儿科研究

Trends in narcotics and sedative use during mechanical ventilation of preterm infants in Canadian neonatal intensive care units

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Abstract: Objective Mechanical ventilation (MV) in preterm infants (PTI) causes discomfort. Whether it causes pain is controversial. Meta analysis reviews of published work on PTI during MV have shown no clinically significant impact of opioids on pain scales, and hence not recommended for routine use in neonatal intensive care units (NICUs). Similarly regular use of sedative midazolam is also not recommended. Therefore we hypothesized a downward trend in narcotics and sedatives used in MV of PTI in NICUs. This study aimed to assess trends of sedatives and narcotics use during MV of PTI in Canadian NICUs during 2004-2009. **Methods** PTI born at gestational age (GA) of <35 weeks requiring invasive MV for >24 hours were identified retrospectively from the Canadian Neonatal Network database for 2004-2009. PTI were excluded if moribund on admission, had major congenital anomalies, surgery (except laser eye surgery), necrotizing enterocolitis, chest tube or history of maternal narcotic abuse. PTI were classified according to whether they received any narcotics (morphine, fentanyl, methadone, sufentanyl, meperidine, alfentynl and codiene) or sedatives (chloral hydrate, midazolam, lorazepam, phenobarbital, pentobarbital, ketamine and propofol) for >24 consecutive hours during MV. Trends of narcotics and sedatives were assessed using the Cochrane-Armitage Trend test separately for PTI born at <29 and 29-34 weeks of GA. **Results** Among 5 638 study subjects, 2 169 (38.5%) received narcotics and 897 (15.9%) received sedatives. The most common narcotics were morphine (62.2%) and fentanyl (63.8%) and sedatives were phenobarbital (44.9%) and chloral hydrate (44.2%). A significant decreasing trend (P<0.01) in the use of any sedatives during MV was observed in PTI <29 and 29-34 weeks of GA. However, the use of any narcotics during MV increased significantly (P=0.03) among PTI <29 weeks of GA, and no change in trend was detected for PTI born at 29-34 weeks of GA. **Conclusions** The use of sedatives during MV in PTI born at <35 weeks of GA was positively affected, however the narcotics use during MV remained constant for PTI born at 29-34 weeks, and increased in extremely low GA group (less than 29 weeks) suggesting evidence based practice change was not observed during the study period. **[Chin J Contemp Pediatr, 2018, 20(1): 5-11]**

Key words: Narcotic; Sedative; Mechanical ventilation; Trend; Preterm infant

加拿大新生儿重症监护病房早产儿机械通气期间麻醉镇痛药和镇静剂应用趋势的回顾性研究

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中文概要：早产儿气管插管有创机械通气可引起患儿不适，但是否导致疼痛仍存有争议。已发表的荟萃分析显示，早产儿机械通气期间应用麻醉镇痛药并未减轻患儿疼痛。因此，不推荐对新生儿重症监护病房（NICU）机械通气早产儿常规应用麻醉镇痛药和镇静剂。假设目前加拿大 NICU 早产儿机械通气过程中麻醉镇痛药和镇

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静剂的使用呈下降趋势。该研究回顾性分析了 2004~2009 年间出生胎龄 <35 周、需要有创机械通气 > 24 h 的早产儿接受镇静剂和麻醉镇痛药使用的趋势。入院时处于濒死状态、先天畸形、需要外科手术（除外眼科激光手术）、坏死性小肠结肠炎、胸腔置管引流或孕母有麻醉药品滥用史的早产儿不纳入该研究。根据早产儿是否接受麻醉镇痛药（如吗啡、芬太尼、美沙酮、舒芬太尼、杜冷丁、阿芬太尼和可待因等）或镇静剂（如水合氯醛、咪达唑仑、劳拉西泮、苯巴比妥、戊巴比妥、氯胺酮和丙泊酚）以及早产儿胎龄（胎龄 <29 周和胎龄 29~34 周）分组，采用 Cochrane-Armitage 趋势分析方法评估早产儿麻醉镇痛药和镇静剂的应用趋势。5638 名早产儿符合纳入标准，其中 2169 名（38.5%）应用了麻醉镇痛药，897 名（15.9%）应用了镇静剂，722 名（12.8%）同时接受了麻醉镇痛药和镇静剂治疗。最常用的麻醉镇痛药是吗啡（62.2%）和芬太尼（63.8%）；最常用的镇静剂是苯巴比妥（44.9%）和水合氯醛（44.2%）。镇静剂的使用在胎龄 <29 周和胎龄 29~34 周两组早产儿中均呈明显的下降趋势（P<0.01）；但胎龄 <29 周组早产儿麻醉镇痛药的使用显著增加（P=0.03），胎龄 29~34 周组麻醉镇痛药的使用未发现明显的趋势变化。

经历有创机械通气的新生儿有疼痛感受吗？机体会产生应激反应吗？据成人有创通气的研究结果报道，约 25% 的 ICU 患者出院后仍记得在 ICU 住院期间的感受，并承认经历气管插管和有创机械通气的过程是很痛苦的。然而，现实中很难区分患者的疼痛感受是由于 ICU 住院期间的有创通气引起，抑或是因在 ICU 住院期间躯体的疾病或其他因素所致。同理，对于住院期间早产儿皮质醇水平的升高，是由于疾病的严重程度或因机械通气引起的疼痛和 / 或应激所致同样很难鉴别。查阅大量文献发现，有创机械通气期间麻醉镇痛药或镇静剂的使用并没有减轻患者的痛苦，然而药物潜在的不良反应却令人担忧。但目前在 NICU 住院早产儿有创机械通气过程中，给患儿应用麻醉镇痛药或镇静剂仍然是很普遍的现象。

该研究数据来自于加拿大新生儿协作网，该协作网覆盖了加拿大全国范围内 30 家三甲医院。样本量大，数据收集方法有效、可靠，这是该研究的主要优势。其主要不足在于机械通气早产儿没有明确的应用镇静或麻醉镇痛药物的指征，一些分析只能是从现有的数据外推。此外，该研究早产儿上机过程中其他非药物镇痛替代措施的应用，也可能会高估或低估麻醉镇痛药 / 镇静剂的作用。其他的影响因素还包括：缺乏疾病的严重度、上机时间以及麻醉镇痛 / 镇静药物应用的评估依据，以及研究资料未能收集到上机过程中环境因素或非药物干预措施减轻患儿不适 / 应激 / 疼痛的数据，所以不能对机械通气过程中麻醉镇痛 / 镇静剂使用趋势做出更为深入的解释。目前，令人担忧的是，机械通气过程中接受阿片类药物镇痛的早产儿是受药物不良反应影响的高风险人群，而这些药物在这个群体中的应用又呈现增加趋势；但如果对 NICU 住院早产儿经历的疼痛和应激不予管理，也会对其神经系统发育产生近期和远期的不良影响。因此，在临床实践中，必须对早产儿的疼痛采用量表进行评估，根据循证医学指南指导麻醉镇痛药和镇静剂的应用，从患儿舒适的角度制定治疗和护理方案。

尽管麻醉镇痛药和镇静剂可能的潜在不良反应的否定证据也逐渐增加，但加拿大新生儿医师仍然担忧机械通气早产儿连续应用麻醉镇痛药和镇静剂以及肌松剂的不良反应。用非药物的措施减轻机械通气患儿的不适 / 应激 / 疼痛的研究日益增多并受到广泛的关注，且有巨大的应用前景。一些在研的、旨在减轻早产儿上机过程中经历的中等程度的疼痛 / 应激、同时又尽可能限制药物不良反应并考虑到对患儿远期神经发育影响药物的研究已经得到批准。另外，住院新生儿经历的慢性疼痛也引起了许多学者的重视，且也成为一个新兴的研究热点，需要学者们开展更深入的研究。

小结：加拿大 NICU 胎龄 <35 周的机械通气早产儿镇静剂的使用呈下降趋势，临床应用遵循了循证医学的证据，但麻醉镇痛药的使用在胎龄 29~34 周早产儿组并没有变化，且超低胎龄早产儿组（胎龄 <29 周）麻醉镇痛药的使用呈增加趋势。加拿大的新生儿医师在决定是否给有创机械通气的早产儿使用麻醉镇痛 / 镇静剂时是慎重的，但该研究结果显示加拿大 NICU 早产儿机械通气期间麻醉镇痛药的使用并没有呈下降趋势，其原因尚需进一步深入研究。

［关键词］ 麻醉镇痛药；镇静剂；机械通气；趋势；早产儿

（摘译：贵州省妇幼保健院 刘玲）

Introduction

There is good evidence demonstrating that neonates in neonatal intensive care units (NICUs) experience pain, and surgical procedures without analgesia has adverse effects on long-term psychosocial development[1-2]. However, controversy remains in two areas: when it comes to determining whether mechanical ventilation leads to pain in neonates and what impacts (positive or negative) sedatives/analgesics have when used for the mechanically ventilated neonate[3-4].

Opioids are the most commonly used medication in the NICU for ventilator related discomfort/stress/pain. A meta-analysis of the efficacy of pain management from opioids during MV in neonates reports the outcome as underwhelming[5]. In the subgroup of very preterm infants born at <32 weeks of gestational age (GA) hypotension and a longer time to reach full enteral feeds were present in the

morphine group compared to placebo. Therefore in the absence of significant clinical benefit and the potential for increased adverse effects routine use opioids in ventilated neonates is not advised and opioid use should be reserved for circumstances when clinical signs of pain are present[5].

Benzodiazepines, primarily midazolam, are the second most common medication studied in mechanically ventilated neonates, although there is a paucity of randomized controlled trials examining the use of benzodiazepines for this purpose. A meta-analysis of sedation with midazolam in neonates found insufficient evidence to recommend use and raised safety concerns, particularly neurological side effects[4,6-8]. Although there are a handful of other sedative/analgesics used for sedation/analgesia in ventilated neonates including phenobarbital, chloral hydrate, ketamine and propofol, none of these medications have been evaluated specifically for sedation and/or pain relief in mechanically ventilated neonates.

The objective of this study was to investigate the trends in sedative and narcotic use during mechanical ventilation in Canadian NICUs from 2004 through 2009. We selected this time period mainly because there was uniform data during that time frame and the methods of data collection were significantly altered after 2010.

Methods

This observational study examined data from infants born at <35 weeks of GA admitted to the NICUs contributing data to the Canadian Neonatal Network (CNN) during 2004-2009. The CNN maintains a national database from 30 hospitals with coverage of greater than 90% of the tertiary NICU beds in Canada. At each participating site, trained abstractors collect chart data from all NICU admissions according to common guidelines. Details of data collection and data management have been published elsewhere[9].

Infants were excluded if born with major congenital anomalies, deemed moribund, required pain management for surgical procedures (excluding laser eye surgery), had necrotizing enterocolitis or presence of a chest drain, had seizures and had a history of maternal narcotic abuse.

Study subjects included remaining infants who received invasive ventilation for greater than 24 hours. Eligible infants were categorized according to whether they received sedatives, narcotics, both or neither for greater than 24 hours consecutive hours during mechanical ventilation. The combined simultaneous exposure to narcotics/sedatives and mechanical ventilation for >24 hours was used as the calculated variable for use of narcotics and/or sedatives for mechanical ventilation since no independent variable exists in the CNN database. Narcotics included in the database are morphine, fentanyl, methadone, sufentanyl, meperidine, alfentynl and codeine. Sedatives included in the database are chloral hydrate, midazolam, lorazepam, phenobarbital, pentobarbital, ketamine and propofol.

Study variables were defined according to the Canadian Neonatal Network manual[10]. GA was defined as the best estimate based on early prenatal ultrasound, obstetric examination and obstetric history followed by pediatric estimate in that order unless postnatal pediatric estimate of gestation differed from the obstetric estimate by greater than 2 weeks. In that case, the pediatric estimate was used.

Temporal trends regarding use of sedatives and narcotics during ventilation was analyzed using the Cohrane-Armitage Trend Test separately for infants born at less than 29 weeks and infants born at 29 to 34 weeks of GA. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary NC) and statistical significance was evaluated using two-sided *P* values at the 5% testing level.

Results

A total of 12 415 infants less than 35 weeks of

GA were admitted to participating NICUs required invasive mechanical ventilation for great than 24 hours from 2004 to 2009. Of this population 5 002 infants were excluded base on exclusion criteria of this study, leaving 7 413 infants eligible for analysis of narcotics or sedative exposure during mechanical ventilation. There were 1 775 mechanically ventilated infants excluded from the cohort because they received narcotics or sedative for less than 24 hours. The final cohort included 5 638 infants; 897 (15.9%) infants received sedatives and 2 169 (38.5%) infants received narcotics. There were 722 (12.8%) infants in the cohort who received both narcotics and sedatives.

For infants less than 35 weeks of GA from 2004 to 2009, it was found there was no trend in narcotics use (P=0.11) and a decreased trend in sedative use (P<0.01). The trend in decreased sedative use was maintained for subgroup analysis by less than 29 weeks and 29-34 weeks of GA. For narcotics use the absence of trend was maintained in the subgroup 29-34 weeks of GA. However, for the subgroup of less than 29 weeks a significant trend towards increased utilization was identified (P=0.03) (Figure 1).

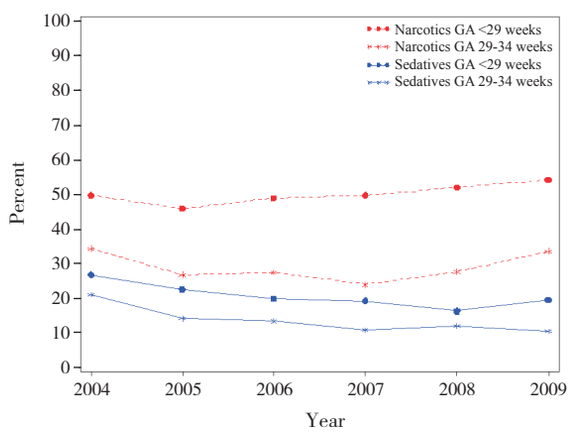

Figure 1 Trends in narcotics and sedatives usage during mechanical ventilation

For infants receiving narcotics during mechanical ventilation the most frequently utilized pharmaceuticals were fentynl (63.8%) and morphine (62.2%), while meperidine and codeine were less used (0.3% and 0.1% respectively). For infants receiving sedatives, the utilized pharmaceuticals included phentobarbitol (44.9%), chloral hydrate (44.2%), midazolam (37.9%), lorazepam (12.9%), ketamine (1.4%), and propofol (0.2%).

Discussion

Is invasive mechanical ventilation painful and/or stressful on neonates? Adult studies tell us that about 25% of ICU patients remember their stay in ICUs and found intubation and ventilation distressing[11]. However, it is difficult to differentiate distress of ventilation from the distress of being in ICUs and other components of care. Ill preterm infants have high cortisol levels, although it is difficult to differentiate if this due to the severity of illness or distress/stress/pain from ventilation or both[12]. Literature evaluating the use of narcotics or sedatives during mechanical ventilation have failed to produce evidence of clinically significant reduction in pain and has raised concerns for adverse effects[3-4]. However the practice of using narcotics and sedatives during mechanical ventilation is common in the NICU. In this study across participating NICUs in Canada 54% of mechanically ventilated infants received narcotics and/or sedatives for greater than 24 hours.

Sedatives were utilized less commonly during mechanical ventilation compared to narcotics and we observed a decreased trend in sedative use over time. Concerns from the literature of inadvertent harm from sedatives may have had an influence on clinical practice in Canada. As the most studied sedative in this population we hypothesized that benzodiazepines would be the most commonly used sedatives; 37.9% of infants on sedatives received midazolam and 12.9% received lorazepam. However, the highest sedatives utilized in this cohort were phenobarbital (44.9%) and chloral hydrate (44.2%). There are no evidence-based trials describing the use of these pharmaceuticals for sedation in mechanical ventilation in neonates. Chloral hydrate has been primarily described for use in non-painful procedural sedation

such as radiological procedures[13]. Historically chloral hydrate had been used frequently as a sedative-hypnotic for infants 'fighting the ventilator'[14]. Chloral hydrate is converted to tricholoroethanol, which is also metabolically active[15]. There has been a case report of encephalopathy from chloral hydrate in a neonate resulting from high concentrations of tricholoroethanol[16]. Therefore it is recommended that this pharmaceutical be used with caution in neonates[12]. Phenobarbital is the preferred therapy for seizure control in neonates and has been used in combination with opioids for reducing excitability in neonatal abstinence syndrome[17]. Antenatal and postnatal phenobarbital was previously thought to protect against intraventricular hemorrhage, however Cochrane reviews do not support these hypothesis[18-19]. In addition postnatal phenobarbital in these studies lead to prolonged duration of mechanical ventilation[19]. It is possible that some of the decreased trend observed in this analysis is secondary to a decrease in use of postnatal phenobarbital to prevent intraventricular hemorrhage. Studies in developing animals have raised serious concerns about neuronal apoptosis with phenobarbital[20]. Phenobarbital reduces the power of spontaneous activity transients (SATs) in the preterm brain encephalogram; SATs are important in preterm brain growth[21-22].

The literature does not support routine preemptive use of narcotics in the management of ventilated preterm infants[17]. Despite a lack of evidence of benefit and potential harm there has not been a substantive decrease in the use of narcotics during mechanical ventilation. Over the six year period of time 28% infants 29-34 weeks of GA in this cohort received narcotics. For infants less than 29 weeks there was a significant trend towards increase use of narcotics with 54% of infants receiving them. The difference between GA may partially be explained by the argument that extremely preterm infants are exposed to a higher number of stressful and painful procedures during their stay in NICUs and therefore require more analgesia[23]. However, we are unable to further elaborate on this hypothesis with our study design. Preemptive use of morphine in very preterm infants during mechanical ventilation is associated with hypotension and longer duration to establish full enteral feeds[24]. Studies evaluating the long-term neurodevelopmental impact of narcotics use are conflicting and complicated by factors such as off label morphine exposures and a variety of dosing regimens[25-28]. Fentanyl was the most commonly utilized narcotics in this cohort of mechanically ventilated infants (63.8%), closely followed by morphine (62.2%). The high representation of fentanyl in our analysis may be secondary to its common use in protocols for rapid sequence intubation for neonates[29].

The main strengths of our study include the large sample size of infants from a national cohort, which has valid and reliable methods of data collection. The main weakness of our study is that the database does have a specific variable to represent that mechanical ventilation was the indication for sedative or narcotics use. Therefore a variable was extrapolated from existing data. Since the main outcome was to compare the trend overtime any bias as a result of this limitation should be equally distributed. Utilization of a surrogate measure could have implications for overestimating or underestimating the use of narcotics/sedatives during mechanical ventilation in Canadian NICUs. Several variables such as severity of illness, duration of ventilation, indication for medications and pain/sedation scale data are lacking to further explore explanations for the trends observed in narcotics and sedative use during mechanical ventilation. Our data does not capture any environmental or non-pharmacological interventions aimed at reducing discomfort/stress/pain during mechanical ventilation. A change in the data variables collected for sedatives and narcotics from 2010 onwards, prevents us from reliably analyzing the trend of narcotics/sedatives use during mechanical ventilation beyond 2009 hence the limitation of the study period until 2010.

Recent evidence may have contributed to a

decreased trend in sedative use during mechanical ventilation and studies are under way to answer this question. It is of concern that the population reported to be at the highest risk of adverse side effects from opioids during mechanical ventilation, are more likely to be receiving them. Untreated pain and stress in the NICU environment has short and long-term consequences; however narcotics and sedatives used to manage pain and stress are not without consequences to short and long-term development. Therefore it is essential to implement use of validated pain and sedation scales to assess pain/stress and nursing driven comfort protocols in mechanically ventilated neonates along with development of evidence based policies/guidelines for patient management including narcotics and sedative use[30]. Concern has been raised for the continuing use of narcotics, sedative and paralytics in ventilated preterm infants by neonatologists in spite of mounting negative evidence[31]. The utilization of non-pharmacological measures is vastly under studied in mechanically ventilated neonates and therefore it remains a potentially under utilized resource to decrease neonatal discomfort/stress/pain. Ongoing research into pharmaceuticals to moderate pain/stress for neonates during mechanical ventilation while limiting harmful effects and considering long-term outcomes is warranted. Chronic pain is an emerging field in neonatal patients and requires ongoing investigation.

In conclusion, sedative use in ventilated PTI in Canadian NICUs appears to be following the evidence and trending downwards, however a high exposure to phenobarbitol and chloral hydrate are described. On the other hand narcotics use has not changed in PTI born at 29 to 34 weeks of GA and increased in the extremely low GA group (less than 29 weeks) suggesting neonatologists in Canada were selective in their application of evidence based practice when it comes to narcotics and sedative use in their respective units[32]. It would be interesting to explore further the reasons why.

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