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Premedication for neonatal endotracheal intubation: results from the EPIPPAIN study

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ABSTRACT (262 words)

Objectives: To describe the frequency and nature of premedications used prior to neonatal endotracheal intubation. To confront observed practice with current recommendations. To identify risk factors for the absence of premedication.

Design, Setting and Patients: Data concerning intubations were collected prospectively at the bedside as part of an observational study collecting around-the-clock data on all painful or stressful procedures performed in neonates during the first 14 days of their admission to 13 tertiary care units in the region of Paris, France between 2005 and 2006.

Interventions: Observational study.

Measurements and Main Results: Specific premedication prior to endotracheal intubation was assessed. Ninety one intubations carried out on the same number of patients were analysed. The specific premedication rate was 56% and included mostly opioids (67%) and midazolam (53%). When compared to recent guidance from the American Academy of Pediatrics, used premedications could be classified as "preferred" (12%), "acceptable" (18%), "not recommended" (27%) or "not described" (43%). In univariate analysis, infants without a specific premedication when compared to others were younger at the time of intubation (median age: 0.7 *vs* 2.0 days), displayed significantly more frequent spontaneous breathing at the time of intubation (31% *vs* 12%) and a higher percentage of analgesia for all other painful procedures (median values : 16% *vs* 6%). In multivariate analysis, no factor remained statistically significant.

Conclusions: Premedication use prior to neonatal intubation was not systematically used and when used it was most frequently inconsistent with recent recommendations. No patient- or centre-related independent risk factor for the absence of premedication was identified in this study.

INTRODUCTION :

Endotracheal intubation is a frequent procedure in neonates. Premedication including an analgesic and/or a sedative agent is considered crucial to decrease pain and discomfort(1), to facilitate intubation(2, 3) and to decrease adverse reactions such as bradycardia(2) or increased intracranial pressure(4). In older children(5) and adults(6), emergency tracheal intubation is usually performed after adequate anesthesia which frequently includes the combination of a central analgesic, a sedative and a neuromuscular blocker. In neonates, no consensus guidelines exist regarding the optimal drug or drug combination. Recent guidance for the clinician from the American Academy of Pediatrics (AAP) recommends the systematic use of rapid onset premedication except for emergent intubation during resuscitation(7).

In spite of the need to provide effective sedation and/or analgesia, implementation of a systematic efficient premedication in Neonatal Intensive Care Units is extremely heterogeneous as illustrated by declarative surveys reporting frequencies of systematic premedication ranging from 34%(8) to 93%(9) in different countries(8-12). Unfortunately, declarative surveys do not always provide reliable information and it is possible that an overestimation of premedication use is declared in this type of study. One observational study in France showed that 63% of neonates hospitalised in intensive care units did not receive any premedication prior to intubation(13). In the United Kingdom a recent observational study conducted in three tertiary neonatal units showed that premedication was used for 94% of intubations(14). In this latter study, morphine was the most commonly used drug in spite of its known prolonged action delay(15) and the lack of evidence supporting its superiority to placebo(16). These results suggest a large potential for practice improvement and underline the importance of epidemiological studies describing actual practices and possible gaps between these and knowledge.

In 2005 and 2006, a large regional longitudinal study (EPIPPAIN) was conducted in 13 tertiary care centres to collect epidemiological data on neonatal pain(17). The present study was part of the EPIPPAIN study and was carried out in order to (i) describe the frequency and type of premedication used prior to endotracheal intubation, (ii) compare observed premedication practice to current recommendations, and (iii) identify factors associated with the absence of premedication use.

Our hypothesis were that premedication rate would be low and rarely in accordance with published evidence. We also hypothesized that factors associated with the absence of premedication would be similar to those observed for the absence of analgesia for other painful procedures in the EPIPPAIN study(17).

PATIENTS AND METHODS

Study design

Detailed methods were previously reported(17). The EPIPPAIN study (Epidemiology of Procedural Pain in Neonates) was designed as a prospective observational study to collect around-the-clock bedside data on all painful or stressful procedures performed in neonates admitted to the participating units. All 14 tertiary care centres, neonatal intensive care units (NICUs) and pediatric intensive care units (PICUs), in the Paris Region were invited to participate and 13 accepted the invitation. During the first 14 days of admission to the participating units, prospective data were collected on all neonatal procedures causing pain, stress, or discomfort with the corresponding analgesic therapy. Inclusion criterion was neonatal admission to the unit during the recruitment period, including preterm neonates younger than 45 postconceptional weeks and term neonates younger than 28 days. There were no exclusion criteria for these neonates. Demographic data, type, and duration of respiratory

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support, sedative and analgesic drugs administered concomitantly or right before the procedure, and conditions related to each procedure (type, hour of the day) were collected. We also recorded repeated procedure attempts for procedures requiring more than 1 attempt before successful completion. Intubations were extracted from the initial database for specific analysis. In order to ensure independency between observations, only the first episode of intubation was considered for analysis if multiple intubations were performed in the same infant at different time points.

Specific premedication definition

Specific premedication was defined by the use of central nervous system depressants through IV or intranasal routes. Non-pharmacological analgesia such as sucrose or comforting measures was not considered as specific analgesia for intubation. Oral or intra-rectal routes were not considered as specific analgesia either because the onset delay related to these routes was considered too long. If an infant was receiving continuous intravenous sedation or analgesia at the time of intubation without additional treatment immediately prior to intubation, that was not considered as specific premedication. Two groups were defined: the group of intubations performed with a specific premedication (Premed group) and the group of intubations performed without any specific premedication (No premed group).

Studied variables

The EPIPPAIN study showed that the following factors were independently associated with the use of analgesia during a painful procedure(17): gestational age, type of respiratory support, parental presence, type of procedure, surgery, day of admission at the time of procedure, time of the day (day: 7:00 am to 6:59 pm, night: 7:00 pm to 6:59 am), continuous analgesia and clinical risk index for babies (CRIB) score(18). Another study has shown lower

rates of premedication in preterm compared to term neonates(13). Among factors studied in the EPIPPAIN study, we discarded parental presence since no intubation was performed in the presence of parents. We also discarded surgery during hospital stay because it could occur after the intubation procedure in an either expected or unexpected situation and could therefore not be considered as a factor influencing the clinician's decision.

We studied other parameters to further explore possible influence of global pain management at a patient- or centre-level on premedication use:

- For all patients, we calculated the frequency of specific analgesia for all other painful procedures except intubation as a proxy for global analgesia management.

- ICU type (NICU or PICU).

- Centres were divided into two groups, above or below median, according to the frequency of analgesia for all procedures. This variable was created as a proxy for global pain management within a single unit.

- Existing written protocol on premedication for neonatal endotracheal intubation at the time of the study.

We collected from the database the availability of an intravenous access in patients from the No Premed group. We also collected the time sequence of procedures when patients had no IV access at the time of intubation. These data were used to explore potential practical barriers to drug injection.

The number of intubation attempts was compared between groups. Distribution of the frequency of specific premedication was compared between centres.

Guidance used as reference

In the Premed group the guidance from the American Academy of Pediatrics was the reference to classify premedication regimen as "preferred", "acceptable", "not recommended"

or "not described"(7). Although this guidance applies only to nonemergent intubation and our study included all intubations, we considered that the majority, if not all, intubations carried out with a specific premedication in our study (Premed group) were nonemergent intubations. Emergent intubations are usually performed without premedication. Although this guidance was publised after the study was performed, it included all drugs recommended in the guidelines published in 2001(19) except for ketamine. It also included other drugs that were not mentionned in the previous recommendations and was the first to classify premedication regimens.

Statistical analysis

Chi-squared or Fisher's exact tests were used to compare categorical variables and distribution of premedication among centres. For continuous variables, data were analysed with t-tests for normally distributed variables, and Mann-Whitney U tests for non-normally distributed variables. The infant and center characteristics of the Premed group and No premed group were compared for infants and centres characteristics in univariate analysis. A p value < 0.05 was considered significant. Multivariate analysis to identify factors associated with the absence of premedication was performed by creating a binary logistic regression model including all variables identified with a p value < 0.20 from univariate analysis. Analyses were performed with SPSS, version 19.0 (SPSS Inc. Chicago, IL, USA).

Ethics

The local committee for the protection of human subjects reviewed the study protocol. Because this was an observational study with no changes in the standard of care, the human subjects committee established that further approvals or parental consent were not required according to French law. The computerized data collection was approved by the French Data

Protection Authority (Commission Nationale de l'Informatique et des Libertés).

RESULTS

During the study period 430 infants were admitted to participating units. A total of 101 tracheal intubations were performed in 91 patients (10 infants were intubated twice). Ninety-one intubations were analysed (only the first intubation was considered for analysis in infants with two intubations). In 51 cases (56 %) a specific premedication was administered before intubation. No intubation initially attempted without premedication was ultimately performed with a premedication. We found 13 different types of premedication regimens (Table 1). Opioids were the most commonly used drugs and were used in 34 (67%) of 51 premedications. Opioids used included sufentanil (n=13), nalbuphine (n=8), fentanyl (n=8) and morphine (n=6 including 1 in combination with fentanyl). Midazolam was the only benzodiazepine used and it was the second most frequent premedication. It was used in 27 (53%) of 51 premedications including 26 by the IV route and 1 by the intranasal route. Propofol was used alone in 4 occurrences (8% of premedications) and a neuromuscular blocker was used once in association with sufentanil. Overall, an association of drugs was used in 17 cases (33%).

Adequacy of administered premedication with current recommendations is summarized in Table 1. The majority of premedications consisted in "not described" protocols (43%). "Preferred" and "acceptable" premedications as defined by the AAP accounted for 30% of premedications.

Characteristics of the Premed and No premed groups are shown in Table 2. The median age at intubation was significantly lower in the No premed group than in the Premed group (0.7 *vs* 2.0 days, p=0.04). Spontaneous breathing was more frequent in the No premed group than in

the Premed group (32% *vs* 12%, p=0.02). The median percentage of analgesia for all other painful procedures was significantly higher in the No premed group than in the Premed group (16% *vs* 6%, p=0.03). All other studied variables did not differ between groups. Forteen out of 40 (35%) intubations and 13 out of 51 (25%) intubations were performed in the No premed and the Premed groups respectively, while the neonate was receiving a continuous sedation-analgesia at the time of intubation (p=0.36). Continuous infusions of sedative and/or analgesics included morphine, fentanyl, sufentanil, nalbuphine and midazolam in both the no premedication group and the premedication group. Thus, of all 91 intubations, 26 (29%) were carried out with neither continuous sedation and/or analgesia nor specific premedication right before intubation. In the No Premed group 34 (85%) infants had an available intravenous access at the time of intubation. Of the 6 infants who had no IV access at the time of intubation, 4 had an umbilical venous catheter or a peripheral line placement within the 60 minutes following the intubation procedure.

Rates of premedication use were significantly different among centres (p=0.04) (Figure 1). Multivariate analysis including age at intubation (aOR=1.01, [95%CI, 0.98 ; 1.05]), daytime *vs* nighttime (aOR=1.65, [95%CI, 0.65 ; 4.17]), spontaneous breathing *vs* ventilatory support (aOR=0.46, [95%CI, 0.14 ; 1.53]) and percentage of analgesia for all other painful procedures (aOR=0.99, [95%CI, 0.97 ; 1.00]) did not identify any independent factor associated with the absence of premedication use.

DISCUSSION

This prospective, around-the-clock, observational study on "real life" practice found that, in intensive care centres of the biggest French region, 44% of intubations were performed without any specific prior analgesia or sedation confirming our hypothesis of low premedication rate. Twenty-nine per cent of intubations were carried out with neither

continuous sedation and/or analgesia nor specific premedication prior to intubation. These

painful and stressful awake intubations were performed although it has been shown for

decades that they may cause hypoxemia(20), bradycardia(21) and intracranial

hypertension(22). The participation of 13 of all 14 centres in this region ensure that the

results are representative of neonatal intensive care in the Paris region and they probably also

reflect national practices(17).

The 56% rate of premedication for endotracheal intubations found in this study is higher than

the 37% rate reported in French intensive care units in 2001(13) but it is still lower than the

74% rate from a declarative survey performed in 2003(12).

We found 13 different regimens used in 51 premedications. Similarly, an Australian survey

found 7 different drug combinations used routinely and another one carried out in the UK

reported 14 different drug combinations(11). Opioids were the most frequently used drugs for

premedication. Although fentanyl has been the most extensively studied opioid for intubations

in neonates(23-25), sufentanil and nalbuphine were the most frequently used opioids. Very

few studies have been reported with sufentanil or nalbuphine in neonates. Sufentanil has been

shown to have satisfactory hemodynamic(26) and respiratory(27) tolerance in preterm

neonates. Nevertheless, to date, no publication has reported the efficacy or tolerance of

sufentanil for neonatal tracheal intubation. Nalbuphine is an agonist-antagonist opioid that

induces less respiratory depression than morphine in adults due to its ceiling effect(28) but it

has never been prospectively assessed in the neonate. Although morphine is very popular in

some countries such as the United Kingdom(9, 14), it was rarely used in our study. There is

no evidence in the literature supporting its use for tracheal intubation(16, 29). Midazolam

was the most frequently single drug used prior to tracheal intubation in our study. This

leading position among all drugs in France in this setting was already observed by Simon *et*

al. in 2001(13). The wide popularity of midazolam for intubations in neonates contrasts with the lack of evidence sustaining its use. A randomised controlled trial studying midazolam and atropine as a premedication prior to intubation was prematurely interrupted because of frequent severe adverse events(30). In combination with remifentanil no such adverse events were observed in a limited number of patients(31, 32). Midazolam has been popular in France possibly because of its mild sedative effects, which allow the persistence of spontaneous breathing that can be reassuring for the operator. Propofol was used in 4 out of 51 (8%) premedicated intubations in our study. This drug might become popular among neonatologists because of its ease of use (single drug, short effect)(31, 33). However, concerns have been raised about its hypotensive effect in preterm infants(34, 35). Nalbuphine and propofol are currently used off-label because data are insufficient to permit drug approval for prescription in neonates. Furthermore, the generic status of opioids, midazolam and propofol considerably reduces the financial interest that pharmaceutical companies would have to promote trials in order to obtain term-specific data or neonatal marketing authorization.

Overall, the practices observed in our study were rarely in adequacy with published evidence or current recommendations. We categorized practices according to recommendations issued after our observational study was carried out. This choice could be argued. We, nevertheless, decided to use this guidance as a reference because it was the only one classifying drugs as "recommended", "acceptable" or "not recommended". Concerning differences between guidelines, the recent guidance that we used did not include ketamine as previous recommendations from the AAP published in 2001(19) did. Ketamine use was, in fact, never observed in our study. Also, the guidance from 2010 is less restrictive than the previous one since it recommends more drugs. In addition, publications existing at the time of our study had already shown the advantages and disadvantages of different drug combinations. For

example, it had been strongly suggested that midazolam should not be used as a single drug for premedication(30). In our study, midazolam was used in 25% of premedicated intubations. It had also been advocated in 2001 that the combination of a synthetic opioid and a muscle relaxant had one of the best benefits/risks ratios(36). This combination was observed only once in our study. The majority (43%) of drug or drug combinations that were observed have not been reported in the literature for intubation in the neonate. At the time of the study no national guidelines existed. In order to avoid misuse or underuse of drugs, it seems necessary that national authorities and scientific societies issue guidelines on this topic; this would contribute to the implementation of evidence-based practice. The lack of recommendations can probably explain the observed heterogeneity in practice. The observed results suggest, as well, a possible insufficient medical knowledge of practitioners on this topic.

In univariate analysis, we found that the absence of specific premedication was more frequent in infants who were younger. Premedication was also less frequent in infants who were not receiving respiratory support as compared to those who were receiving non invasive ventilation or invasive ventilation (reintubations) at the time of intubation. It was less frequent in those infants who received a higher rate of analgesia for all other painful procedures. We do not have a clear explanation for this practice. The existence of a local written protocol was not associated with a more frequent use of premedication in our study. In the multivariable analysis we confirmed the direction of the associations reported above including increasing age at intubation, daytime vs nighttime, spontaneous breathing vs ventilatory support and percentage of analgesia for all other painful procedures. However no factor remained significant in this multivariable analysis, suggesting a lack of power to identify predictive factors. Multivariate analysis did not identify patient- or centre-related factors associated with the absence of premedication rejecting our hypothesis that factors already identified in the

EPIPPAIN study would be confirmed. The fact that factors that were associated with analgesia use in the Epippain study were not associated with premedication use in the present study suggests that intubations were not managed as other painful procedures. We should state, however, that our model probably lacked other relevant variables because operator-related variables (experience, apprehension) and circumstances of intubation (urgent, semi-urgent or planned) were not collected. It is plausible that other relevant factors were not included in our model. This model could also have been underpowered to show more subtle associations. These limitations should be kept in mind when interpretating the results. A potential barrier to premedication administration could have been unavailable IV access. Our results do not support this hypothesis since 85% of infants in the No Premed group already had an IV access at the time of intubation. Only 6 infants were intubated without an IV access. We do not know the exact reasons for this but we speculate that an IV line was not placed prior to intubation because either an immediate intubation was needed as part of resuscitation following an acute deterioration or the clinician estimated that obtaining an IV access to provide a specificpremedication before intubation in order to manage pain and stress was not a priority. Interistingly, in adult patients awake intubation is only considered if the patient is completely unresponsive, nearly dead or in cardiac arrest(6). Awake intubations are still common in neonates, though in 2001, a consensus statement from the International Evidence-Based Group for Neonatal Pain concluded that "tracheal intubation without the use of analgesia or sedation should be performed only for resuscitation in the delivery room or for life-threatening situations associated with the unavailability of intravenous access"(19). It is possible that concerns about prolonged intubation procedures or unsuccessful intubations lead clinicians to avoid premedication in some occasions. These concerns contrast with published data showing that premedication decreases procedure time(25, 29, 33) and increases success rates(2, 32, 37). We did not find a difference in gestational age of premedicated and no

premedicated infants. This differs from the findings of Simon *et al.* who reported a lower rate of premedication in preterm infants(13). Though in univariate analysis premedicated infants were older (median age of 2 days) than non premedicated ones (median age of 0.7 days), in multivariable analysis this difference was not significant.

Since the EPIPPAIN study was not initially designed to study risk factors for the absence of premedication prior to neonatal endotracheal intubation, we consider that our study has two main limitations. First we were not able to collect specific information on either the indication of intubation or the experience of the operator which could be considered as potential risks factors for the absence of premedication. We did not collect information on the tolerance of intubation either. Thus, we ignore which were elective, semi-urgent or urgent intubations. In fact, there is currently neither a clear definition of emergent intubation nor clear evidence of usual rates of emergent intubation in neonates admitted to NICUs. For exemple, two randomised controlled trials comparing two types of premedication for nonemergent neonatal intubation reported rates of emergent intubation without providing precise criteria for this categorisation. Roberts *et al.*(25) reported a 21% rate of emergent intubation in the NICU. In another study, Choong *et al.*(38) found a 86% rate of emergent intubation. Objective criteria for defining emergent intubations are required so that results of future studies can be compared. We speculate that in our study emergent intubations did not explain the observed lack of premedication because in our empirical experience emergent intubations do not account for 45% of all intubations in the NICU or PICU; we do not have, however, published data to support this speculation.

Second, our study had insufficient power to show subtle differences between intubations performed with and without premedication. For instance, unlike a previously reported study(2), we did not observe a difference in the number of attempts according to the use of

premedication. Moreover, since the overall success rate for the first intubation attempt was higher (69%) than in other studies, the left margin for success rate improvement was limited

Our results highlight the difficulties of implementing evidence-based practices in daily care. Effective interventions to change practice are not clearly recognized yet but require identification of barriers as a first step(39). Possible barriers to good practice include historical local practices as illustrated by the persistence of midazolam use in France and the variability observed among units. It has been reported that in many areas of medicine there is a large chasm between what we know and what we do(40, 41). This seems to be true of efforts to improve neonatal pain management as well and supports the need to develop tools to translate research into practice. In one study, collaborative use of quality improvement methods resulted in the creation of logical, efficient, and effective processes to improve neonatal pain management(40). At our regional level, we have used our results to try to increase the rate of premedication for neonatal intubations. We have presented our results to staff representing participating centres and discussed about possible strategies. Further communication and education on this subject is planned in future national medical congresses.

Efforts should be made to reach a consensus and to establish and spread sound guidelines concerning premedication prior to neonatal tracheal intubation. The involvement of national and international scientific societies seems crucial for this process. Tailored collaborative interventions should also be carried out in order to implement evidence-based practice at bedside and to decrease painful experiences in hospitalised neonates.

REFERENCES

1.	Carbajal, R., B. Eble, and K.J. Anand: Premedication for tracheal intubation in neonates: confusion or controversy? *Semin Perinatol* 2007; 31:309-17

2.	Oei, J., R. Hari, T. Butha, et al: Facilitation of neonatal nasotracheal intubation with premedication: a randomized controlled trial. *J Paediatr Child Health* 2002; 38:146-50

3.	Bhutada, A., R. Sahni, S. Rastogi, et al: Randomised controlled trial of thiopental for intubation in neonates. *Arch Dis Child Fetal Neonatal Ed* 2000; 82:F34-7

4.	Stow, P.J., M.E. McLeod, F.A. Burrows, et al: Anterior fontanelle pressure responses to tracheal intubation in the awake and anaesthetized infant. *Br J Anaesth* 1988; 60:167-70

5.	McAllister, J.D. and K.A. Gnauck: Rapid sequence intubation of the pediatric patient. Fundamentals of practice. *Pediatr Clin North Am* 1999; 46:1249-84

6.	Reynolds, S.F. and J. Heffner: Airway management of the critically ill patient: rapid-sequence intubation. *Chest* 2005; 127:1397-412

7.	Kumar, P., S.E. Denson, and T.J. Mancuso: Premedication for nonemergency endotracheal intubation in the neonate. *Pediatrics* 2010; 125:608-15

8.	Sarkar, S., R.E. Schumacher, S. Baumgart, et al: Are newborns receiving premedication before elective intubation? *J Perinatol* 2006; 26:286-9

9.	Kelleher, J., P. Mallya, and J. Wyllie: Premedication before intubation in UK neonatal units: a decade of change? *Arch Dis Child Fetal Neonatal Ed* 2009; 94:F332-5

10.	Whyte, S., G. Birrell, and J. Wyllie: Premedication before intubation in UK neonatal units. *Arch Dis Child Fetal Neonatal Ed* 2000; 82:F38-41

11.   Hancock, S., S. Newell, J. Brierley, et al: Premedication for neonatal intubation: current practice in Australia and the United Kingdom. *Arch Dis Child Fetal Neonatal Ed* 2000; 83:F77

12.   Walter-Nicolet, E., C. Flamant, M. Negrea, et al: [Premedication before tracheal intubation in French neonatal intensive care units and delivery rooms]. *Arch Pediatr* 2007; 14:144-9

13.   Simon, L., M. Trifa, M. Mokhtari, et al: Premedication for tracheal intubation: a prospective survey in 75 neonatal and pediatric intensive care units. *Crit Care Med* 2004; 32:565-8

14.   Venkatesh, V., V. Ponnusamy, J. Anandaraj, et al: Endotracheal intubation in a neonatal population remains associated with a high risk of adverse events. *Eur J Pediatr* 2011; 170:223-7

15.   Upton, R.N., T.J. Semple, and P.E. Macintyre: Pharmacokinetic optimisation of opioid treatment in acute pain therapy. *Clin Pharmacokinet* 1997; 33:225-44

16.   Lemyre, B., J. Doucette, A. Kalyn, et al: Morphine for elective endotracheal intubation in neonates: a randomized trial [ISRCTN43546373]. *BMC Pediatr* 2004; 4:20

17.   Carbajal, R., A. Rousset, C. Danan, et al: Epidemiology and treatment of painful procedures in neonates in intensive care units. *Jama* 2008; 300:60-70

18.   The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. *Lancet* 1993; 342:193-8

19.   Anand, K.J.: Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001; 155:173-80

20.   Marshall, T.A., R. Deeder, S. Pai, et al: Physiologic changes associated with endotracheal intubation in preterm infants. *Crit Care Med* 1984; 12:501-3

21.   Kelly, M.A. and N.N. Finer: Nasotracheal intubation in the neonate: physiologic responses and effects of atropine and pancuronium. *J Pediatr* 1984; 105:303-9

22.   Friesen, R.H., A.T. Honda, and R.E. Thieme: Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. *Anesth Analg* 1987; 66:874-8

23.   Barrington, K.J. and P.J. Byrne: Premedication for neonatal intubation. *Am J Perinatol* 1998; 15:213-6

24.   Hamon, I., J.M. Hascoet, A. Debbiche, et al: Effects of fentanyl administration on general and cerebral haemodynamics in sick newborn infants. *Acta paediatrica* 1996; 85:361-5

25.   Roberts, K.D., T.A. Leone, W.H. Edwards, et al: Premedication for nonemergent neonatal intubations: a randomized, controlled trial comparing atropine and fentanyl to atropine, fentanyl, and mivacurium. *Pediatrics* 2006; 118:1583-91

26.   Nguyen The Tich, S., M.F. Vecchierini, T. Debillon, et al: Effects of sufentanil on electroencephalogram in very and extremely preterm neonates. *Pediatrics* 2003; 111:123-8

27.   Seguin, J.H., A. Erenberg, and R.D. Leff: Safety and efficacy of sufentanil therapy in the ventilated infant. *Neonatal Netw* 1994; 13:37-40

28.   Gal, T.J., C.A. DiFazio, and J. Moscicki: Analgesic and respiratory depressant activity of nalbuphine: a comparison with morphine. *Anesthesiology* 1982; 57:367-74

29.   Norman, E., S. Wikstrom, L. Hellstrom-Westas, et al: Rapid Sequence Induction is Superior to Morphine for Intubation of Preterm Infants: A Randomized Controlled Trial. *J Pediatr* 2011; 159:893-899 e1

30.   Attardi, D.M., D.A. Paul, D.J. Tuttle, et al: Premedication for intubation in neonates. *Arch Dis Child Fetal Neonatal Ed* 2000; 83:F161

31.   Penido, M.G., D.F. de Oliveira Silva, E.C. Tavares, et al: Propofol versus midazolam for intubating preterm neonates: a randomized controlled trial. *J Perinatol* 2011; 31:356-60

32.   Pereira e Silva, Y., R.S. Gomez, O. Marcatto Jde, et al: Morphine versus remifentanil for intubating preterm neonates. *Arch Dis Child Fetal Neonatal Ed* 2007; 92:F293-4

33.   Ghanta, S., M.E. Abdel-Latif, K. Lui, et al: Propofol compared with the morphine, atropine, and suxamethonium regimen as induction agents for neonatal endotracheal intubation: a randomized, controlled trial. *Pediatrics* 2007; 119:e1248-55

34.   Papoff, P., M. Mancuso, E. Caresta, et al: Effectiveness and safety of propofol in newborn infants. *Pediatrics* 2008; 121:448; author reply 448-9

35.   Welzing, L., A. Kribs, F. Eifinger, et al: Propofol as an induction agent for endotracheal intubation can cause significant arterial hypotension in preterm neonates. *Paediatr Anaesth* 2010; 20:605-11

36.   Duncan, H.P., N.J. Zurick, and A.R. Wolf: Should we reconsider awake neonatal intubation? A review of the evidence and treatment strategies. *Paediatr Anaesth* 2001; 11:135-45

37.   Feltman, D.M., M.G. Weiss, P. Nicoski, et al: Rocuronium for nonemergent intubation of term and preterm infants. *J Perinatol* 2011; 31:38-43

38.   Choong, K., K. AlFaleh, J. Doucette, et al: Remifentanil for endotracheal intubation in neonates: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2010; 95:F80-4

39.   Gurses, A.P., J.A. Marsteller, A.A. Ozok, et al: Using an interdisciplinary approach to identify factors that affect clinicians' compliance with evidence-based guidelines. *Crit Care Med* 2010; 38:S282-91

40.   Sharek, P.J., R. Powers, A. Koehn, et al: Evaluation and development of potentially better practices to improve pain management of neonates. *Pediatrics* 2006; 118 Suppl 2:S78-86

41.   McGlynn, E.A., S.M. Asch, J. Adams, et al: The quality of health care delivered to adults in the United States. *N Engl J Med* 2003; 348:2635-45