Premedication for neonatal intubation: Current practice in Saudi Arabia

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ABSTRACT

Background: Despite strong evidence of the benefits of rapid sequence intubation in neonates, it is still infrequently utilized in neonatal intensive care units (NICU), contributing to avoidable pain and secondary procedure-related physiological disturbances. **Objectives:** The primary objective of this cross-sectional survey was to assess the practice of premedication and regimens commonly used before elective endotracheal intubation in NICUs in Saudi Arabia. The secondary aim was to explore neonatal physicians' attitudes regarding this intervention in institutions across Saudi Arabia. **Methods:** A web-based, structured questionnaire was distributed by the Department of Pediatrics, Umm Al Qura University, Mecca, to neonatal physicians and consultants of 10 NICUs across the country by E-mail. Responses were tabulated and descriptive statistics were conducted on the variables extracted. **Results:** 85% responded to the survey. Although 70% believed it was essential to routinely use premedication for all elective intubations, only 41% implemented this strategy. 60% cited fear of potential side effects for avoiding premedication and 40% indicated that the procedure could be executed more rapidly without drug therapy. Treatment regimens varied widely among respondents. **Conclusion:** Rates of premedication use prior to non-emergent neonatal intubation are suboptimal. Flawed information and lack of unified unit policies hampered effective implementation. Evidence-based guidelines may influence country-wide adoption of this practice.

Key words: *Endotracheal intubation, neonate, premedication, sedation*

INTRODUCTION

Increasing evidence suggests that intubation of neonates, particularly in an awake state, is an invasive and potentially distressing procedure associated with a variety of undesirable hemodynamic complications such as hypoxemia, bradycardia, hypertension, and intracranial hypertension.[1-5] In premature infants, it could result in intraventricular hemorrhage with potential long-term sequelae.[6,7] Although premedication for endotracheal intubation may lower the incidence of side effects, it is currently underused due to lack of adequate training or standardization among neonatal units. The implementation of an effective premedication protocol and policy for nonemergent intubation may minimize intubation-related injuries and the number of unsuccessful intubations and may also improve physiological stability in the newborn.[8,9]

AIMS AND OBJECTIVES

The primary objective of this cross-sectional survey was to assess the practice of premedication and regimens commonly used before elective endotracheal intubation. The secondary aim was to explore neonatal physicians' attitudes regarding this intervention in institutions across Saudi Arabia prior to the development of evidence-based recommendations.

METHODS

An 8-item web-based structured questionnaire [Table 1] was developed using pertinent items on the topic from a literature review[10-12] and those of local relevance. The content of the survey items were reviewed for clinical sensibility and clarity and initially agreed upon by two neonatologists (RM and KA-F) and subsequently the neonatologists in their respective

Table 1: Questionnaire items employed for the survey

1.	Role of the surveyed clinician?	o	NICU consultant
		o	NICU specialist
2.	Do you administer premedication prior to elective intubation?	o	Yes
		o	No
3.	Do you believe it is essential to use premedication routinely for elective intubation?	o	Yes
		o	No
	If you answered No, please indicate why?	o	Neonates don't feel pain during intubation
		o	Potential side effects
		o	Others (please specify)
4.	Does your unit have a written policy/guidelines for premedication use?	o	Yes
		o	No
5.	Does your unit have guidelines for drug reversal?	o	Yes
		o	No
6.	What medication do you use or prefer to use? Please check the respective drug(s) and document the names of the corresponding drug(s) utilized?	o	Opiates
		o	Benzodiazepine
		o	Atropine
		o	Paralytic agent (Muscle relaxant)
		o	Others
7.	Please note the drug(s) used in sequence for premedication		
8.	Do you have a monitoring policy during and after the premedication	o	Yes
		o	No

centers. It was then distributed, in a single-stage, non-randomly via E-mail, to neonatal physicians and consultants across 10 largest academic, tertiary, neonatal intensive care units (NICU) in Saudi Arabia. The questionnaire was designed to elicit responses regarding knowledge, attitudes, and the use of premedication for elective intubation, existing guidelines, or policies for the procedure with appropriate monitoring and treatment of potential side-effects, and the medication sequence employed. Data were collected using the online survey engine (available at www.surveymonkey.com) and was analyzed using the corresponding survey software. The questions were brief, each addressing a single issue and the majority evoked a simple "yes" or "no" response to the closed ended questions. The questionnaire and the survey protocol were forwarded to the Ethics Review Board at King Khalid University Hospital and consent for participation in the study was exempted.

Statistical analysis

Descriptive, quantitative, outcomes were sought to investigate main reasons for withholding premedication prior to non-emergent intubation. All frequency and cross-tabulation analyses were performed using the statistical software package IBM SPSS® 19.0, 2010. Descriptive statistics were utilized to analyze the variables and are reported as percentages in the respective tables.

RESULTS

Of the 80 neonatal clinicians contacted by E-mail, 68 (85%) responded to the survey [Table 2].[11-16] The majority of the respondents were consultants (75%), whereas 25% were full-time physicians practicing in tertiary level NICUs.

Of the respondents, only 28 (41%) were using premedication prior to intubation, but all respondents were in agreement that neonates feel pain during the intubation procedure. Forty-eight (70%) of the 68 surveyed individuals believe it is essential to use premedication as a standard protocol for all elective intubations.

Most clinicians who did not offer premedication prior to elective intubation in their practice had concerns regarding potential side effects (60%) and believed that intubation was quicker without premedication (40%) and raised lack of proper training (5%) as a reason for withholding or withdrawing the routine use of premedication.

Only 18/68 (26%) respondents indicated the availability of a written policy/protocol in their units and of those 22% had guidelines for drug reversal.

The most common medications administered were midazolam (40%), fentanyl (36%), and morphine (30%): 30 respondents used these agents for premedication, either alone or in combination. Nine (30%) of those who utilized premedication prior to intubations administered neuromuscular blockade in the form of suxamethonium or rocuronium. Only seven of 30 individuals (23%) reported the combined use of atropine, sedation, and neuromuscular blockade to facilitate intubation.

DISCUSSION

Although there is growing and compelling evidence that premedication for non-urgent intubations in neonates is safer, quicker, and more effective than awake intubations,[17-19] this procedure is not performed routinely for all neonates.[10,11,13,14]

Recently, the American Academy of Pediatrics (AAP) guidelines for rapid sequence intubation (RSI) in neonates provided standardization regarding the use of premedication for elective or semi-elective intubation.[9] Our study indicates that most elective intubations are performed in the NICU as awake intubations (without the use of sedatives, analgesia, or muscle relaxant) despite the cumulative evidence of the benefits of premedication. Data

Table 2: Summary of the surveys on premedication for elective intubation

Author/Year/Country	Ziegler 1992/USA[13]	Whyte/2000/UK[11]	Vogel/2000/Canada[14]	Simon/2004/France[10]	Sarkar/2006/USA[12]	Kelleher/2009/UK[15]	Chaudhary/2009/UK[16]	Mosalli/2012/Saudi Arabia
Type of survey	Mailed Q	Phone Q	Mailed Q	Mailed Q	E-Mail Q	Phone Q	Phone Q	Electronic Q
Surveyed (*n*) clinicians/units/neonates	101 NICUs	239 NICUs	263 neonatologists	140 neonates in 75 NICUs	100 neonatal program directors	221 NICUs	50 NICUs	10 NICUs/80 neonatal physicians
Response rate (%)	74	30	57	76	78	93	98	85
Attitudes regarding the use of PM explored	No	No	No	No	No	No	No	Yes
PM used routinely (%)	3	14	<25 (<30 wks) 51 (30-37 wks) 75 (>37 wks)	37	43	93	90	41
Existing written policy/guidelines for PM (%)	N/A	14	N/A	20	24	76	77	35
Existing guidelines for PM drug reversal	N/A	N/A	N/A	N/A	N/A	N/A	N/A	29%
Choice of medications Opiate/hypnotic (%)	Sedative not specified	Morphine alone (40)	Morphine (53); FNT (67)	MDZ alone	Morphine or FNT alone (57); MDZ alone (7)	Morphine (80) alone or combined	Morphine (67) FNT (27)- alone or combined	Morphine (30); FNT (36); MDZ (40)
Use of muscle relaxants (%)	0	14	45	2.9	25	78	82	30
Atropine±Sedation and paralysis (%)	0	24	N/A	30	11.5	66	50	23
Identified barriers to PM	Atropine only	N/A	Yes	N/A	N/A	N/A	N/A	Yes

FNT - Fentanyl; MDZ - Midazolam; N/A - Not addressed; NICU - Neonatal intensive care unit; PM - Premedication; Q - Questionnaire; Wks - Weeks

from published surveys compared to our results are shown in Table 2. In our survey, only 41% of the respondents routinely use medication prior to intubation [Table 2]. Our findings for under-use of premedication are consistent with reports from other countries.[10-13,20]

Awake intubation is associated with severe distress and acute changes in vital signs with accompanying heart rate variability, elevated blood pressure, oxygen desaturation, and intracranial hypertension.[21-23] In addition, prolongation of the procedure, even with a successful first attempt, the requirement for multiple attempts, and the potential for supraglottic injury may further adversely impact the preprocedure normalcy of a newborn's clinical status.[3,6,11,24] Table 3[1,6,19,24-28] summarizes randomized controlled trials detailing the effects of non-medication-assisted neonatal intubation compared to various premedications in the treatment arms of the respective studies.

The present study identifies some likely reasons for not offering premedication to neonates. These may include concerns over adverse effects and lack of familiarity regarding the benefits of premedication. This is consistent, for the most part, with the barriers reported by Ziegler[13] but was not evident in a large multicenter observational study by Simon *et al*.[10] Strategies to overcome misconceptions about the routine utilization of premedication should address both personal and knowledge-deficient barriers through continuous education, identify appropriate treatment regimens (RSI medications) together with raising awareness of potential side effects and specific methods of drug reversal.[8,9,14] Tracheal intubation without the use of analgesia or sedation should be performed only for urgent or life-threatening situations such as resuscitations in the delivery room or sudden, unanticipated cardio-respiratory decompensation in the NICU setting.[29]

The results reported indicate considerable variation in drugs used for premedication. Sedatives (mostly midazolam) are being increasingly used without an analgesic. Midazolam should not be administered alone without an analgesic because it causes serious complications which include hypotension, compromised cardiac output, and cerebral blood flow velocity.[30-32] In an animal model, rabbits premedicated with fentanyl followed by induction of anesthesia with midazolam resulted in hypotension with reduced quality of recovery.[33] Similar reports of hypotension with the combined use of fentanyl and midazolam have been documented during electrophysiological procedures,[34] and sedation and anesthesia.[35,36] Moreover, in preterm

babies (<33 weeks gestational age), midazolam is associated with adverse neurological events.[37,38] Only 23% reported using atropine and only 30% of the respondents use a muscle relaxant. In addition, our study highlighted a lack of consensus about the best combination and drug sequences for RSI. Although there are a variety of premedication protocols reported in the literature for elective neonatal endotracheal intubation, there is no clear agreement about the best combination or sequence of drug administration.[9] In general, premedication drugs should have a rapid onset and short duration of action and comprise anticholinergic agents to reduce the incidence of bradycardia. A reasonable regimen that is widely utilized involves a vagolytic agent such as atropine, an opioid (fentanyl or remifentanil) to ameliorate intubation-induced pain and hemodynamic instability, followed by a paralyzing agent (suxamethonium or rocuronium) to facilitate neuromuscular blockade.[9,17,23,39] Of note, although the efficacy of suxamethonium as a short-duration muscle relaxant has been proven in randomized clinical trials,[2,19,28] its association with rare adverse events such as hyperkalemia, malignant hyperthermia, cardiac arrhythmias, and rhabdomyolysis make it a less preferred agent compared to rocuronium and vecuronium.[9] A proposed algorithm for premedication is shown in Figure 1.[9,39-42]

It is evident from this survey that the majority of neonatal units lack a detailed written policy for routine premedication which encompasses a guideline for drug dosage, appropriate drug combinations, a specific sequence for drug administration, and recommendations for drug reversal of unanticipated side effects.[9]

The policy should encourage the use of pre-prepared syringes to reduce errors and time consumed for drug preparation.[23] Such policies would standardize the approach to elective intubation and reduce variability in practice among neonatal practitioners in the same unit and across units.

Documentation must become a prerequisite for the procedure and be strongly enforced in the respective institutions. A structured outline must minimally include route of intubation (oral/nasal), endotracheal tube size, premedication drug doses, time of administration, vital signs before and after the onset of the procedure, and side effects with appropriate corrective treatment recorded. Neonatal teams involved in the intubation should communicate as the medications are given. They should comprise one recorder to document events occurring, a single individual allocated to medication delivery who should also be ready to provide drug antidotes if required,

and a skilled practitioner who should be dedicated for airway management (use of bag-mask ventilation/laryngeal mask or supraglottic backup airway, laryngoscopy, and intubation).[9] Antidotes such as naloxone, an opioid antagonist for the reversal of opioid-induced respiratory depression, flumazenil to counteract the effect of benzodiazepines, and neostigmine with atropine to combat the adverse effects of rocuronium should be immediately available. It is important to recognize that there is no reversal agent for suxamethonium and the infant should be ventilated until the short-duration depolarizing action terminates.

To the best of our knowledge, this is one of the few well-conducted surveys on premedication in the region and one of the few studies that has evaluated attitudes and actual practice of neonatal physicians, in an attempt to identify possible barriers to premedication use. The limitations of this study include the use of a self-developed instrument that was founded on reliable scientific literature but not previously validated, the absence of pilot testing of the survey, and a possible response selection bias despite the 85% response rate. The positive assets are an assessment of physician attitudes and barriers which were coupled in the same survey and an examination of drug reversal policies [Table 2]. Hopefully, our data will prove valuable in establishing regional multidisciplinary, educational strategies in order to streamline an evidence-based approach to premedication and ensure both changes in attitude and
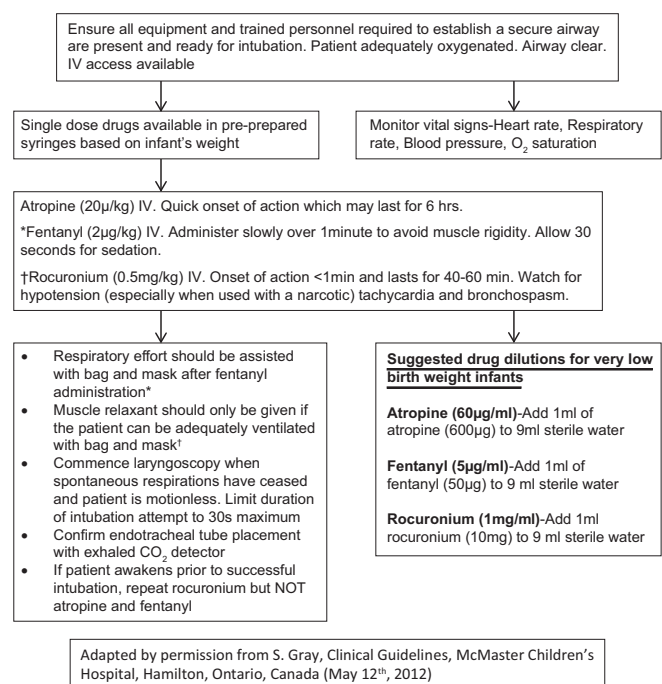

Figure 1: Algorithm for premedication for elective endotracheal intubation in neonates

Table 3: Randomized controlled trials detailing the effects of non-medication-assisted neonatal intubation

Author country	RCT study year	Premedications versus placebo	Sample size population	Significant effects documented	Comments
Hassid[25] (France)	2007	Sevoflurane 2-5% versus no medication	*n*=33 Term and preterm	Less bradycardia and hypertension in sevoflurane versus awake group; 8.3% versus 44.4% (*P*<0.01) and 25% versus 56.3% (*P*=0.04). Intubation easier in the sevoflurane group with no movements (95.5% versus 28%; *P*<0.005) and glottis visualization (73% versus 33%; *P*=0.013).	Random allocation not true randomization. Small number of subjects, less than precalculated power sample size. No significant differences in systemic blood pressure (BP) or number of desaturation episodes. Fewer adverse events in the sevoflurane group
Lemyre[26] (Canada)	2004	Morphine 0.2 mg/kg IV or placebo (0.9% sodium chloride), for elective intubation	*n*=60 Term and preterm infants	No effect on severity of physiological disturbance during intubation (heart rate[HR], BP) No significant difference in number of attempts or duration of procedure between the two groups.	Small sample size; Different levels of individual expertise performing the intubations; Variations in time of preoxygenation and positive pressure ventilation.
Oei[19] (Australia)	2002	Morphine 100 mg/kg, atropine 10 mg/kg, and suxamethonium 1 mg/kg versus awake intubation	*n*=20 Gestational age (range): 25-40 weeks. Weight (range): 650-3660 g	Significantly greater decrease in HR in the premedicated group; 29 beats/min (bpm) versus awake 68 bpm (*P*=0.017). Significantly shorter duration of procedure; premedicated 60 s versus awake 595 s (*P*=0.002). Median number of attempts, more than twice as many attempts in the awake group (*P*=0.01)	Lack of blinding; Small sample size; Groups not completely matched
Bhutada[27] (USA)	2000	Study group (*n*=15); thiopental (6 mg/kg) Control group (*n*=15); physiologic saline	*n*=30; neonates >2 kg at birth requiring semi-elective intubation for management of respiratory failure or before surgery	Significantly less variable HR in study group (mean) -2.0 vs 19 msec; (*P*<0.01) Lesser change in mean BP in thiopental group (mean [Standard Error] -2.9 [1.8] vs 4.4[1.1] mmHg; *P*<0.002) Significantly shorter procedure duration in the thiopental group 2.7±0.37 min vs placebo 5.08±1.1 min (*P*<0.04).	Lack of blinding; Small sample size; Data on 2 infants in the control group and 1 in the study group were lost during acquisition and were excluded from the analysis. No significant differences in oxygen saturation between the two groups during or after intubation
Millar[1] (Canada)	1994	Group 1 (*n*=7); awake intubation Group 2 (*n*=6); thiopentone (5 mg/kg) and succinylcholine (2 mg/kg)	14 neonates aged 1-34 d; Gestation; >32 weeks	Mean rise in anterior fontanel pressure (AFP) significantly higher in awake group (12 vs 3 mmHg; 254% baseline change vs 44% (*P*<0.05). Greater change in HR in awake patients +33 bpm; *P*<0.05. No group differences in systolic BP; however, both groups showed increases in BP (*P*<0.05)	Lack of blinding. Small sample size; Randomization method not well described; Discrepancy in the study age group: abstract (1-34 d); methods section: (1-42 d) Data from one patient was not included in the final result

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Table 3: (*Continued*)

Author country	RCT study year	Premedications versus placebo	Sample size population	Significant effects documented	Comments
Barrington[28] (Canada)	1989	Group 1: awake (*n*=10); atropine (20 mg/kg) Group 2: (*n*=10) succinylcholine (2 mg/kg) plus atropine	20 newborn preterms	Significantly greater rise in intracranial pressure (ICP) in awake vs paralyzed group (41.4±23.3 v 36.8±11.6 cm H_2O; *P*<0.05) Significant increased cerebral perfusion pressure in paralyzed group (mean 39.4-54.2 mmHg) vs awake group Intubation significantly shorter in succinylcholine group (*P*<0.05) 41% increase in systemic BP occurred immediately after administration of succinylcholine (*P*<0.01) No infants in either group suffered bradycardia (HR<100 bpm) during intubation	Lack of blinding. Not true randomization Data on randomized and non-randomized infants who received group 1 protocol were combined Postnatal ages of succinylcholine group were significantly greater
Friesen[6] (USA)	1987	Group 1 (*n*=6); atropine (0.02 mg/kg) (awake intubation) Group 2 (*n*=6); atropine (0.02 mg/kg), pancuronium (0.1 mg/kg), and one of 4 anesthetics [0.75% isoflurane (*n*=3), 0.5% halothane (*n*=1), 20 mg/kg fentanyl (*n*=1), or 2 mg/kg ketamine (*n*=1) with intubation after 10 min of mask ventilation	12 preterm neonates Gestation: 28-36 wk Weight: 920-2250g requiring surgical procedures	AFP increased significantly in awake group 7.7-23.8 cm H_2O (*P*<0.05). Mean increase 197%±158 vs 25%± 41 (Group 2) Systolic BP increased significantly by 20% in awake intubation (*P*<0.05)	Small sample size. Lack of blinding The 4 anesthetics used decrease AFP which may have influenced the outcome. Awake intubation is associated with increased ICP and may be responsible for intraventricular hemorrhage
Kelly[24] (Canada)	1984	Group 1 (*n*=10); control (no medication) Group 2 (*n*=10); atropine (0.01 mg/kg) Group 3 (*n*=10); atropine (0.01 mg/kg) and pancuronium (0.1 mg/kg)	30 neonates with birth weights from 580 to 3450g (25-40 wk)	Statistically significant bradycardia in groups 1 (*P*<0.01) and 2 (*P*<0.01) vs no bradycardia in group 3 (*P*>0.05) In group 3 there was lesser rise in ICP (*P*<0.05) and least changes in HR	Small sample size Lack of blinding All infants experienced an increase in mean BP during intubation No significant differences in systemic BP and transcutaneous PO_2 between groups were noted

regional clinical practice. The ultimate goals perhaps will be best achieved over time as was evident in the surveys conducted across Britain.[15,16]

CONCLUSION

Rates of premedication prior to non-emergent intubation in neonates are suboptimal in Saudi Arabia but the findings are not strikingly dissimilar to the other published surveys. Flawed information and lack of unified unit policy have impeded effective implementation. The findings may also have implications for pediatricians practicing in advanced

level 2 nurseries where the approach to intubation may need standardization. Development of evidence-based guidelines in the format of a position statement, especially if steered through the Saudi Neonatal Society and other similar international pediatric advisory bodies, might garner better support for the widespread utilization of premedication for elective intubation in countries worldwide.

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