



Variability of neonatal premedication practices for endotracheal intubation and LISA in the UK (NeoPRINT survey)

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ABSTRACT

Objective: The NeoPRINT Survey was designed to assess premedication practices throughout UK NHS Trusts for both neonatal endotracheal intubation and less invasive surfactant administration (LISA).

Design: An online survey consisting of multiple choice and open answer questions covering preferences of premedication for endotracheal intubation and LISA was distributed over a 67-day period. Responses were then analysed using STATA IC 16.0.

Setting: Online survey distributed to all UK Neonatal Units (NNUs).

Participants: The survey evaluated premedication practices for endotracheal intubation and LISA in neonates requiring these procedures.

Main outcome measures: The use of different premedication categories as well as individual medications within each category was analysed to create a picture of typical clinical practice across the UK.

Results: The response rate for the survey was 40.8 % (78/191). Premedication was used in all hospitals for endotracheal intubation but overall, 50 % (39/78) of the units that have responded, use premedications for LISA. Individual clinician preference had an impact on premedication practices within each NNU.

Conclusion: The wide variability on first-line premedication for endotracheal intubation noted in this survey could be overcome using best available evidence through consensus guidance driven by organisations such as British Association of Perinatal Medicine (BAPM). Secondly, the divisive view around LISA premedication practices noted in this survey requires an answer through a randomised controlled trial.

What is already known on this topic?

Premedications in various combinations are routinely used across all NNUs. There are clear guidelines for its use in the scenario of a non-emergency intubation in a neonatal setting. Over the last decade use of LISA has become more commonplace with gentle use of non-invasive ventilation with an aim to reduce ventilator induced lung injury and bronchopulmonary dysplasia.

What this study adds

The NeoPRINT survey demonstrated that all NNUs have guidance for non-emergency routine endotracheal intubation (ETI), but the opinion is divided for routine premedication use for LISA in non-invasive ventilation setting. While some feel this will allow smooth LISA delivery, others feel that this may be counterproductive resulting in intubation. There is also a significant variation of practice across various levels of NNUs and even variations attributed to clinician preference.

How this study might affect research, practice, or policy

Abbreviations: BAPM, British association perinatal medicine.; ETI, Endotracheal intubation.; LNU, Lower level/level two neonatal unit or High dependency Unit.; LISA, less invasive surfactant administration.; NICU, Neonatal Intensive care unit/level three neonatal unit or tertiary neonatal unit.; NNU, Neonatal unit (including all the levels); ODN, Operational delivery networks; SCBU, Special care baby unit; Level 1 neonatal unit.

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The NeoPRINT survey demonstrated the need for a recommended consensus guidance for premedications use for ETI across the UK involving national stakeholders such as BAPM. Secondly, the variation and strong feeling around premedication use in LISA should be a basis of developing a randomised controlled trial to answer those questions.

1. Background

The scientific understanding of neonatal pain perception has prompted a renewed interest in the importance of pain management consequent to medical procedures on neonates [1]. Neonatal endotracheal intubation (ETI) and less invasive surfactant administration (LISA) are required for airway management, surfactant administration and assisting ventilation in respiratory insufficiency [2]. To alleviate pain, premedication are commonly used prior to neonatal ETI. Its necessity stems not only from the neonate's experience of pain, but also unwanted physiological effects of ETI, including hypoxaemia, bradycardia, intracranial hypertension, systemic hypertension, and, in rare cases, pulmonary hypertension [3–6]. The different premedications target these problems, leading to effective smooth ETI in a controlled environment [7]. Several trials have demonstrated that the use of premedication can significantly improve intubation conditions and reduce the likelihood of multiple attempts [8–10]. A 2009 survey revealed a national appreciation of this, as 90 % of UK NICUs were found to routinely give premedication before elective intubations [11]. However, the premedication regimen used still varies widely between neonatal units as there is a little consensus on how best to invoke excellent intubation conditions while minimising side effects.

Although considered to be an effective, minimally invasive technique to administer surfactant, LISA requires airway instrumentation with direct laryngoscopy which can cause painful stimuli that might lead to adverse physiological responses. Chaudhary et al. have reported that these adverse effects might be attenuated by using premedication [8]. However, the issue of whether to routinely sedate infants for LISA remains contentious [1,8]. Many centres prefer to use non-pharmacological methods prior to LISA like swaddling and using sucrose which seems to be tolerated and reduces the risk of apnoea known to be associated with some premedication specifically fentanyl [9].

2. Methodology

The Neonatal Premedication practices for LISA and ETI (NeoPRINT) electronic survey was prepared in Qualtrics (Qualtrics XM, Utah, US) and sent via email through the neonatal operational delivery networks (ODNs) and individual units across the UK. The aims were (a) to map standard premedication practices preceding intubation and LISA in different UK NNUs, (b) identify alternative practices in relation to specific situations such as prematurity or underlying cardiac conditions, (c) investigate regional and local variability of current guidelines/clinical practice between NNUs, (d) provide an insight for a review of the safety of premedication by highlighting common side effects encountered in practice as well as any alternative drugs used avoid these side effects.

The NeoPRINT survey comprised of 45 questions (Supplemental Appendix 1) covering preferences of premedication for ETI or LISA, including vagolytics (atropine), analgesics (morphine, fentanyl and remifentanyl), sedatives (midazolam and propofol), muscle relaxants (suxamethonium), dosages given of each of these drugs, adverse reactions, medication preferences in special situations (prematurity and underlying cardiac conditions), and the existence of written premedication guidelines.

The responses were collected over two months period. Inconsistent data within the same NNU was followed up via telephone. The data was analysed using STATA IC 16.0 (STATA Corp LLC, Texas, US) software.

3. Results

The survey ran from 11th November 2021 until 17th January 2022. There were 90 responses in total from 78 different Neonatal Units within the UK, including 1 response from Wales and 6 from Scotland. The response rate was 78/191 (40.8 %). Twelve out of the 15 neonatal networks responded (80 %). 14 (18 %) responses were from SCBU, 31 (40 %) from LNU and 33 (42 %) from NICU. The majority 77/78 (98.7 %) of NNUs had guidelines for ETI premedication.

3.1. NeoPRINT survey results for endotracheal intubation (ETI) practices

The use of vagolytics for ETI varied widely between different hospitals. Of the hospitals using vagolytics, atropine was used in 46 hospitals (74 %). Use of vagolytic premedication is more commonplace in LNU (28/31, 88.9 %) compared to SCBUs (10/14, 75 %) and NICUs (23/33, 71 %). Among those using vagolytics, a third reported using adrenaline if the neonate is seen to have profound bradycardia.

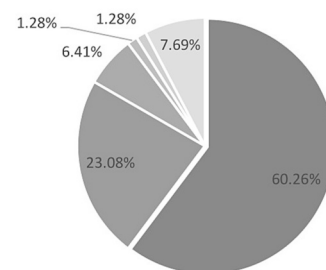
Seven different medication combinations were used for analgesia/sedation across the hospitals, with the most popular individual drugs being fentanyl (47/78, 60.3 %), followed by morphine (18/78, 23 %), and Propofol (5/78, 6.4 %) (Fig. 1). Almost a third of responses (29/90) stated that they had a second-line preference for analgesia/sedative medications, but these were generally personal preferences.

The most common muscle relaxants used in ETI were suxamethonium (63/78, 81 %) and atracurium (11/78, 14.4 %). Most responses (62/78, 78.9 %) stated that they did not have second-line muscle relaxant choices.

NICUs were more likely to use alternative premedication in specific circumstances (5/33, 15.2 %), compared with LNU (4/31, 12.9 %) or SCBUs (1/14, 7 %). Repeat doses were administered by most NNUs (72/78, 92.3 %) when the baby was felt to be active after the first dose, or in cases of prolonged intubation attempts. The number of repeat doses was often attributed to individual preferences. Respondents did not alter practice in specific situations such as congenital heart disease (80/90, 88.8 %). This reflects the variability of individual practices in these situations. Most (84/90, 93.3 %) would not use premedication in emergencies. Adverse reactions were reported by 35/90. 68.6 % of those responders (24/35) stated that they noticed chest rigidity. 70.8 % of those reported chest rigidity particularly after administration of fentanyl.

(39 %) of respondents, with chest wall rigidity after fentanyl use being most noted (24/35, 68.6 %). About half of LNU (16/31) reported adverse events, compared to a third of SCBUs and NICUs (16/47, 34 %).

First Line Analgesia/Sedative Choices for Endotracheal Intubation from Responding Hospitals



■ Fentanyl ■ Morphine ■ Propofol ■ Remifentanyl ■ None ■ Multi-Drug Combination

Fig. 1. First line premedication choices for sedation/analgesia from responding hospitals across the UK.

3.2. NeoPRINT survey results for LISA practices

A Majority of the NNUs (67/78, 85.9 %) reported to perform LISA (Table 1). 35.7 % of SCBUs and 19.3 % of LNUs (6/31) that responded did not perform LISA. Premedication for LISA is used by over half of units performing it (38/67, 56.7 %). Of those that perform LISA, a vast majority (65/67, 97.0 %) had written guidelines. Only 1 SCBU and 1 LNU were lacking written guidelines. 10 different medication combinations were used for LISA (Fig. 2).

When using premedication for LISA, many (56/67, 83.6 %) used a smaller dose compared to that used in ETI. Only two (NICU) hospitals had a second-line preference for premedication; these were clinician preferences. Most LNUs and NICUs used premedication (19/28, 64.3 % and 16/29, 55.7 %, respectively) compared to SCBUs (4/10, 40.0 %) (Table 1).

3.3. Variations in LISA premedication practice at responding NNUs

Around a quarter of the respondents have (21/90, 23 %) noted adverse reactions when using premedication for LISA including apnoea and chest rigidity. (10/32) 31 % of NICUs and (5/29) 17.2 % of LNUs that perform LISA reported that they have adverse reactions. One hospital reported their intention to move away from LISA premedication. There was a variation of preferences within networks; the main source of variation arose between the levels of the NNUs and personal preferences of the clinicians. The most frequently used premedications are detailed in Fig. 3.

4. Discussion

The vast majority of NNUs used premedication for ETI and had guidelines in place. Although premedication practices for LISA were more variable, most NNUs had LISA guidelines. The most common premedications for ETI were suxamethonium, atropine and fentanyl. In contrast, the preference for LISA was fentanyl or morphine. There were variations in clinical practice between different hospitals within trusts, individual hospitals, and between the different levels of NNUs. Further variations were apparent in clinician preferences, which also had an impact on premedication choices.

The widespread availability of guidelines was in keeping with existing literature [8]. Among premedications, vagolytics were less commonly used (62/78, 79.5 %) compared to analgesics/sedatives (77/78, 98.7 %). Within analgesia/sedation, opioids were reported as the most common first-line medication by 84.6 % (66/78) of all NNUs (30/33, 90 % of NICUs). The use of analgesia facilitates faster, less traumatic intubation, which mirrors the findings of a 2013 European survey which reported that 79.8 % of UK NICUs used opioids as part of their premedication regimen for ETI and ventilation [12,13].

Most second-line premedication preferences were determined by clinician choice rather than guidelines, indicating the widespread use of individual judgement in more complicated cases. The most reported adverse effect among all respondents was chest wall rigidity observed with fentanyl use. This is likely due to the more widespread use of

Table 1

Demonstrates variability in premedication use among NNUs performing LISA. Actual number of responses and percentages in (). LISA: Less Invasive Surfactant Administration. NNU: Neonatal unit. SCBU: Special care baby unit. LNU: lower level/level two neonatal unit. NICU: neonatal intensive care unit.

NNU level	Perform LISA without premedication (%)	Perform LISA with premedication (%)	All units performing LISA
SCBU	6 (60.0)	4 (40.0)	10 (14.9)
LNU	9 (32.1)	19 (67.9)	28 (41.8)
NICU	13 (44.8)	16 (55.2)	29 (43.3)
Total (%)	28 (41.8)	39 (58.2)	67 (100)

First line LISA premedication choice across the UK

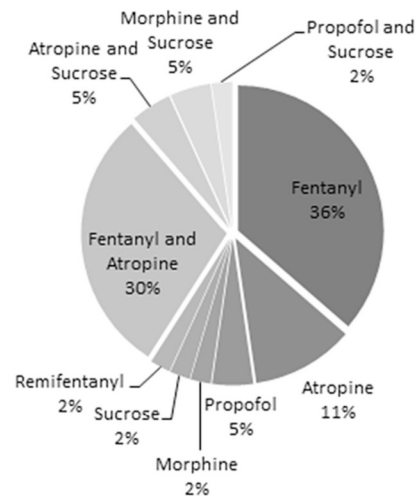


Fig. 2. First line premedication choices for LISA from responding hospitals across the UK.

LISA: Less Invasive Surfactant Administration.

fentanyl compared to other premedication [14]. The use of muscle relaxants for ETI was common among NNUs, with two hospitals opting not to include it as part of their premedication regimen. Suxamethonium and atracurium were most chosen, likely because their widespread use in various medical and surgical scenarios has improved clinician familiarity with the medications [15–17]. The use of a muscle relaxant alongside opioids can reduce the likelihood of chest wall rigidity and further improve intubation conditions, making it likely that this is another driver for clinician preference [13,17–19]. The routine use of suxamethonium reported among NNUs supports similar findings from a 2009 survey [11]. Some of the NNUs do not use vagolytics (24/78, 30.7 %), this is likely due to using single-use premedication such as propofol. Atropine was the most common medication (58/78, 74.4 %), likely due to its extensive use in a variety of trials demonstrating its safety and efficacy [15,16]. Although the proportion of NICUs opting for atropine use (22/33, 66 %) was slightly lower among all NNUs due to use of propofol as single agent; it was considerably higher than the number reported by a previous survey of UK NICUs [8]. The increased likelihood of NICUs using alternative premedication in specific circumstances compared to LNUs is likely due to the increasingly complex patient cases dealt with in such units.

The survey highlighted the variability of LISA practice in different level NNUs. We found that 14 % of the responding hospitals (11/78) across the UK do not perform LISA. There were variations within the same neonatal network, and this was mainly related to local preferences. Among neonatal centres world-wide, there was a significant variation in the use of pharmacological agents to provide infants with analgesia and sedation during the LISA procedure [20]. While some centres opt for a standard approach using medications for LISA, others try to avoid using pharmacological sedation entirely. Furthermore, for centres using medications for LISA, there remains a wide variety of choices for the specific agent used, from fentanyl and morphine, through to propofol and ketamine [20,21]. In the literature, there is convincing evidence for the significant variation in LISA procedure preparation throughout NNUs worldwide [22,23]. Peterson et al. [24], discussed the problem of a standardized approach by using certain medications and doses prior LISA. Applied to individual infants, there is no assurance that the recommended dose will be adequate or not. In some cases, infants exposed to opioids during pregnancy, routine dosing of fentanyl is entirely inadequate [25]. The NeoPRINT survey responses highlighted that there were 7 different medications (fentanyl, atropine, sucrose, propofol,

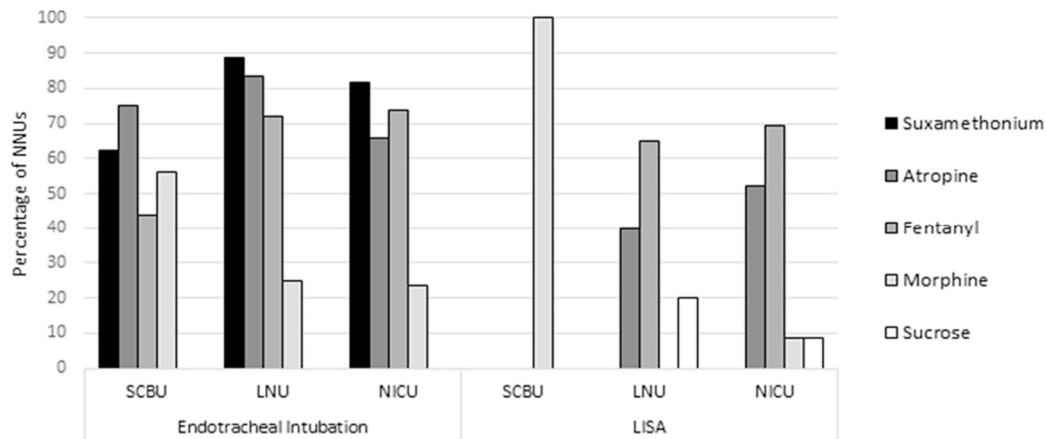


Fig. 3. First line medication choices by neonatal unit level, represented as a percentage of responses from each network.

LISA: Less Invasive Surfactant Administration. NNU: neonatal unit. SCBU: special care baby unit. LNU: lower level/level two neonatal unit. NICU: neonatal intensive care unit.

morphine, caffeine citrate, remifentanyl) used in various combinations in LISA. Fentanyl is the most used medication prior to LISA, followed by combination of fentanyl and atropine. Also, there were different doses used for LISA across the UK (which were lower than the usual doses used for intubation to reduce the side effects) (Fig. 1). SCBUs appear to prefer the use of morphine for intubation and LISA whereas fentanyl was preferred by LNUs and NICUs (Fig. 2). About 23 % of the NNUs (18/78) have reported adverse reactions including apnoea and chest rigidity. Some practices opted to give awake sedation induced with opioids, while keeping naloxone available in case of opioid-related side effects such as apnoea and shallow breathing [26,27].

A variety of medications have been studied for the purpose of analgesia/sedation during LISA; fentanyl, ketamine and propofol were the most frequently used medications to reduce pain scores, however they may interfere with spontaneous breathing [28]. Stress and pain in neonates may have a long-term negative impact on their development, however, medications used for relieving pain or stress have also acute and chronic adverse effects. Thus, practice patterns vary widely as clinicians weigh risks and benefits individually [29]. Additionally, we have found variations determined by the personal preferences of physicians, especially for second-line premedication choices. There are limited data about the personal preferences of the physicians in other countries but there is an ethical explanation of the individualized approach in some NNUs as there are some clinicians who may inaccurately appreciate (over-appreciation or under-appreciation) the extent of the infant's distress [30–33]. A retrospective review by Dekker et al. showed there was improved comfort during LISA when sedation was given ($P = 0.02$), however there was a slight trend towards invasive ventilation when it was used [28]. Most of the centres in Germany preferred to do the first attempt without analgesia and used nonpharmacological methods such as positioning, holding, and/or sucrose solutions [34].

The NeoPRINT survey showed the majority of the NNUs performing LISA had their own guidelines. One hospital specified certain medications based on the gestational age, using atropine and sucrose for neonates with a gestational age less than 34 weeks. A clear communication was made throughout the duration of the survey of how important it was for the NNUs to participate and how relevant the results would be for future clinical practice and research. The survey received responses from NNUs across the UK providing nationwide data that aided in the generalisability of the results. We cannot comment on the extent to which NNUs are following trust guidelines if present, and whether practices are similar between different NNU levels within the same neonatal network. Without a complete response rate, we cannot accurately comment on the variation in preferences across the UK.

The information gathered from this survey cannot fully explain the

differences in adverse event reporting between NNUs, thus further qualitative research using semi-structured interviews with the staff should be undertaken to address this. It is also unclear whether use of clinician's preference is due to an absence of detailed alternatives provided within hospital guidelines or whether it is due to the familiarity of various clinicians with different drugs available. The determination of a set of guidelines according to best practice would avoid individuality affecting the quality of care.

5. Conclusion

From the NeoPRINT survey it can be concluded that most NNUs have local guidelines for premedications for endotracheal intubation, although some appear to have their own practice affected by individual clinician preferences. Systematic review and meta-analysis of current literature discussing the variation of the premedication choices and their adverse effects would aid the development of a standardized guidance for practice. National consensus on first-line premedication for ETI should be recommended through guidance driven by organisations such as BAPM. LISA with non-invasive ventilation is increasingly being practiced to reduce the incidence of BPD, however, this survey demonstrates that there is no consensus on use of premedication for this procedure; and this warrants an answer through a randomised controlled trial.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.earlhumdev.2023.105808>.

CRediT authorship contribution statement

E.M. and K.J. designed the survey, performed the analysis and contributed in writing the first draft of the manuscript equally. B.M. verified the collected data and contributed to the first draft of the manuscript. J.B and S.S conceived the idea, supervised the work. All authors discussed the results and contributed to the final manuscript.

Conflicts of interest and sources of funding

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