Premedication with atropine+ketamine vs atropine+ketamine+/-propofol for less invasive surfactant administration: a prospective comparative study

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Background

Less invasive surfactant administration (LISA) is associated with decreased mechanical ventilation and reduced bronchopulmonary dysplasia in premature infants¹. However, analgosedation was rarely used in controlled trials¹ in spite of the known pain and discomfort induced by the laryngoscopy this technique requires.

When we implemented this technique in our unit in 2015, we used routine premedication with atropine+ketamine, which resulted in a relatively high rate of subsequent intubation².

In 2016, we modified our premedication protocol by limiting the dose of ketamine and adding propofol if required.

We hypothesized that this new protocol would reduce the intubation rate.

Objective

To compare the efficacy (pain control) and the tolerance (intubation rate) of a premedication using atropine + ketamine +/- propofol vs atropine + ketamine prior to a LISA procedure.

Methods

Design & Setting

Prospective study in a single level III center's Neonatal Intensive Care Unit comparing 2 periods with different premedication protocols.

Patients

As per local protocol, infants were eligible for a LISA procedure if they met the following criteria:

- Gestational age > 25 weeks + 6 days and < 37 weeks
- Receiving non-invasive ventilation
- Diagnosis of neonatal RDS requiring surfactant administration based on clinical signs and chest Xray

FiO₂ thresholds for surfactant administration were:

- ≥ 0.25 for infants born < 28 weeks
- ≥ 0.30 for infants born ≥ 28 weeks

Contra-indication to a LISA procedure were:

- Pneumothorax
- Hemodynamic instability
- Frequent apnea and bradycardia
- Hypercapnia > 65 mm Hg

Intervention – Local protocol

From March 2015 to November 2016 (KETA period) we used atropine+ketamine titrated by 0.5 mg/kg increments. From November 2016 to March 2018 (KETAPRO period), we used atropine + a single dose of ketamine with an optional single dose of propofol if satisfactory sedation was not achieved.

Drugs' doses used are summarized in Table 1.

Table 1 : Drugs' doses

Drugs	KETA (March 15-Nov 16)	KETAPRO (Nov 16 – March 18)
Atropine (µg/kg)	20	20
Ketamine (mg/kg)	Increments of 0.5 Maximal dose : 3	Unique dose 0.5 if GA < 30 weeks 1 if GA ≥ 30 weeks
Propofol (mg/kg)	-	Unique dose only if adequate sedation was not achieved 5 min after ketamine: 0.5 if GA < 30 weeks 1 if GA ≥ 30 weeks

Results

From December 2016 to March 2018, 18 infants were included in the study and were compared to 40 infants from the previous period. Their baseline characteristics are summarised in Table 2.

Table 2: Baseline characteristics expressed as means (SD)

	KETA (March15-Nov16) n=40	KETAPRO (Nov16– March18) n=18	p
GA at birth, wks	30.1 (2.3)	30.2 (2.9)	0.94
Birth weight, g	1384 (561)	1300 (499)	0.59
FiO ₂ at LISA, %	35 (12)	39 (9)	0.20

The description and tolerance of the LISA procedure in the 2 periods are summarised in Table 3. During the KETAPRO period 15/18 infants received propofol and the doses of ketamine used were significantly reduced as compared to the KETA period.

Table 3: Description of the LISA procedure

	KETA (March15-Nov16) n=40	KETAPRO (Nov16– March18) n=18	p
Median [IQR] ketamine dose, mg/kg	1.5 [1-2.5]	1 [0.5-1]	<10 ⁻⁴
Median [IQR] propofol dose, mg/kg	(1 infant: 2)	0.75 [0.5-1]	-
Apnea, n (%)	19 (48)	9 (50)	0.78
Intubation before LISA, n (%)	7 (18)	3 (18)	1.00
Median [IQR] number of laryngoscopy	2 [1-4]	1 [1-2]	0.42
Desaturation < 85%, n (%)	25 (63)	14 (78)	0.20
Median [IQR] lowest SpO ₂ value, %	59 [20-92]	43 [23-56]	0.06
Intubation < 72h, n (%)	18 (45)	8 (44)	1.00
Pain assessment	n=30	n=16	
Median [IQR] Faceless Acute Neonatal Pain Score (FANS)	2 [2-4]	2 [2-4]	1.00
FANS < 4, n (%)	18 (60)	10 (63)	1.00

Discussion

The optional addition of propofol and the limitation of ketamine's dose was not associated with a decrease in the immediate or delayed intubation rate. We observed a trend towards lower SpO₂ nadirs in the KETAPRO period.

Propofol should probably be used as a single agent with a unique dose in order to improve its respiratory tolerance, as suggested in other studies³⁻⁵.

Conclusion

Obtaining adequate and safe sedation during LISA in challenging. Combining ketamine and propofol had no advantage over ketamine alone in our population.

References

- 1: Aldana-Aguirre et al *Arch Dis Child Fetal Neonatal Ed.* 2017 102(1):F17-F23.
- 2: Bourgoin L et al. *Acta Paediatr.* 2018;107(7):1184-1190
- 3: Dekker J et al. *Arch Dis Child Fetal Neonatal Ed.* 2018 Aug 1. pii: fetalneonatal-2018-315015.
- 4: Descamps CS et al. *Arch Dis Child Fetal Neonatal Ed.* 2017 Sep;102(5):F465
- 5: Dekker J et al. *Neonatology.* 2016;109(4):308-13.