Supplementary Online Content

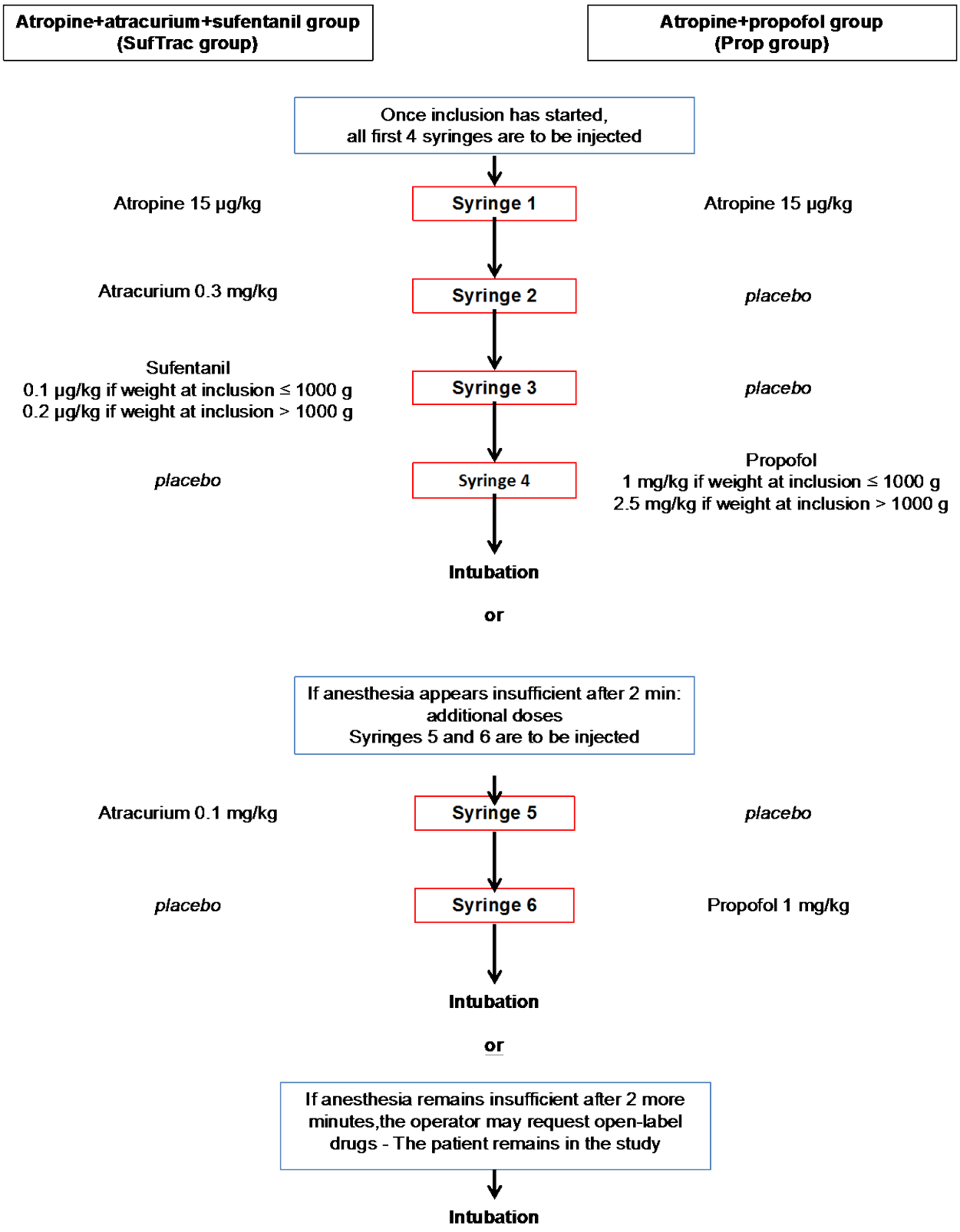
Durrmeyer X, Breinig S, Claris O, et al. Effect of atropine with propofol vs atropine with atracurium and sufentanil on oxygen desaturation in neonates requiring nonemergency intubation. *JAMA*. doi:10.1001/jama.2018.3708

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Detailed reasons for the 2 interruptions in the study

The first interruption occurred when the vials used for propofol's placebo exploded in an autoclave and thus delayed the subsequent production campaign. The second interruption occurred after the first drug manufacturing company (Amatsi, Saint-Augustin, France) unilaterally decided to stop the production with short notice. Another company capable of producing appropriately masked placebo propofol kits was found only in Switzerland (Baccinex, Courroux, Switzerland) after 2 months. Because regulatory rules did not permit the export of opioids or anesthetics across borders, the sponsor asked a complementary French manufacturing company (Theradis Pharma, Cagnes-sur-Mer, France) to produce all items of the study kits, except the placebo for propofol, which was produced in Switzerland. The numerous issues in coordinating the production and obtaining adequate authorizations and guarantees from all parties explain the 19-month interruption.

Supplemental Figure 1: Treatment administration and blinding procedure



Definitions of procedure-related secondary outcomes

Number of attempts

Each insertion of the laryngoscope in the baby's mouth was considered an attempt.

Duration of the procedure

Although the initial definition of procedure duration in the registered protocol was the time between the first laryngoscope insertion and last laryngoscope removal after successful intubation, the variable collected in the clinical research form was defined as the time between first laryngoscope insertion and the fixation of the tube with tape. The data reported correspond to the latter definition.

Time to spontaneous respiratory and limb movement recovery

The exact time of the recovery of spontaneous respiratory movements was collected by the independent observer, based on the trigger logo of the ventilator used for conventional ventilation when the synchronized mode was used or through direct observation if high-frequency oscillation or ventilation was used.

The exact time of recovery of spontaneous limb movements was collected by the independent observer through direct observation of the neonate. The first spontaneous limb movement was considered.

Quality of sedation scale

Data regarding the quality of intubation conditions were collected immediately after completion of the procedure by the operator who successfully intubated the infant, according to the following scale adapted from Hans[1] and Cooper:[2]

- Excellent: Relaxed jaw, open vocal cords, and no movement during endotracheal tube (ETT) insertion
- Good: Relaxed jaw, open vocal cords, mild movements during ETT insertion
- Acceptable: Mild jaw contraction and/or moving vocal cords and/or cough during ETT insertion
- Poor: Jaw contraction or closed vocal cords or intense cough or rigidity during ETT insertion.

Predefined stopping rules

The following stopping rules were established *a priori* and approved by the French regulatory authorities (ANSM). In the event that the number of severe adverse events listed below reached the predefined threshold, the data and safety committee was to request immediately the interruption of the study.

- Occurrence of 2 deaths possibly or certainly attributable to the study drugs
- Occurrence of 3 cardiac arrests requiring chest compression and/or epinephrine administration, possibly or certainly attributable to the study drugs and not to the intubation procedure itself.
- Occurrence of 12 grade 3 or 4 intraventricular hemorrhages according to Papile's classification,[3] within 7 days of inclusion and not preexisting at inclusion.

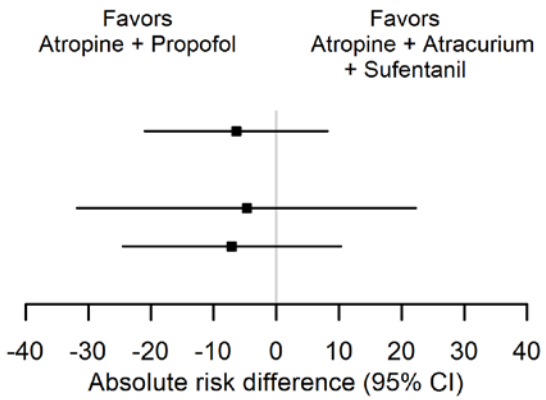
No interim analysis was either planned or performed.

References

1. Hans P, Brichant JF, Hubert B, Dewandre PY, Lamy M. Influence of induction of anaesthesia on intubating conditions one minute after rocuronium administration: comparison of ketamine and thiopentone. *Anaesthesia.* 1999;54(3):276-279.
2. Cooper R, Mirakhur RK, Clarke RS, Boules Z. Comparison of intubating conditions after administration of Org 9246 (rocuronium) and suxamethonium. *Br J Anaesth.* 1992;69(3):269-273.
3. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr.* 1978;92(4):529-534.

Supplemental Figure 2: Subgroup analysis for the primary outcome according to weight at randomization

	Atropine +propofol n/N	Atropine +Atracurium +Sufentanil n/N	Absolute risk difference (95% CI)
Overall	53/89	54/82	-6.4 (-21.0 to 8.1)
Infants <= 1000 g	16/27	16/25	-4.7 (-31.8 to 22.3)
Infants > 1000 g	37/62	38/57	-7.1 (-24.5 to 10.3)



Supplemental Table1: Desaturation time per treatment group after imputing different values for infants without the primary outcome

Outcomes	**Atropine +propofol group (N=89)**	**Atropine +atracurium +sufentanil group (N=82)**	**Adjusted absolute differences: Atropine+propofol group *minus* Atropine+atracurium+ sufentanil group (95% CI)[a]**	***P* value[b]**
Primary outcome				
SpO2<80% for > 60 sec, n (%)	53 (59.6)	54 (65.9)	-6.4 (-21.0 to 8.1)	.38
Duration of SpO2 <80% after imputing different values for infants without the predefined primary outcome[c]				
N with data available	87 (97.8)	81 (98.8)		
Scenario 1 Imputed value for infants without prolonged desaturation= 0 sec				
Median [IQR], min	1.3 [0; 2.9]	1.6 [0; 3.3]	0.0 (-1.2 to 0.0)	.16[d]
Mean (SD), min	1.8 (2.2)	2.8 (3.5)	-1.0 (-1.9 to 0.2)	.02
Scenario 2 Imputed value for infants without prolonged desaturation= 30 sec				
Median [IQR], min	1.3 [0.5; 2.9]	1.6 [0.5; 3.3]	0.0 (-0.8 to 0.0)	.15 [d]
Mean (SD), min	2.0 (2.1)	3.0 (3.4)	-1.0 (-1.8 to 0.2)	.02
Scenario 3 Imputed value for infants without prolonged desaturation= 59 sec				
Median [IQR], min	1.3 [0.98; 2.9]	1.6 [0.98; 3.3]	0.0 (-0.5 to 0.0)	.15 [d]
Mean (SD), min	2.2 (1.9)	3.1 (3.3)	-1.0 (-1.7 to 0.2)	.02

a: Absolute risk difference and mean difference were calculated with a generalized mixed model adjusted for weight at inclusion (≤ 1000 g, >1000 g) taking into account within-center correlation, and median difference with Hodges-Lehmann estimation.
b: p-values were obtained from adjusted generalized mixed models unless otherwise stated
c: In all 3 scenarios, the value “0” was imputed for the 3 randomized infants who were never intubated
d: Kruskal-Wallis test

Supplemental Table 2: Baseline characteristics of participants before and after the 19-month interruption

Characteristics	Patients included in 2012-2014		Patients included in 2016	
	Atropine +propofol group	Atropine +atracurium +sufentanil group	Atropine +propofol group	Atropine +atracurium +sufentanil group
	(N=71)	(N=65)	(N=18)	(N=17)
Median GA at birth [IQR], weeks	30.0 [28.0;34.0]	29.0 [27.0;31.0]	31.0 [27.0;36.0]	28.0 [26.0;33.0]
Median birth weight [IQR], g	1230 [795;2190]	1140 [875;1685]	1570 [900;2550]	1120 [800;1515]
Boys, n (%)	35 (49.3)	45 (69.2)	9 (50.0)	12 (70.6)
Median postnatal age at inclusion [IQR], d	2.0 [1.0;14.0]	2.0 [0.0;11.0]	1.0 [0.0;8.0]	1.0 [0.0;6.0]
Median weight at inclusion [IQR], g	1310 [906;2300]	1260 [990;1685]	1615 [995;2550]	1340 [830;2185]
Weight categories at inclusion, n (%)				
≤ 1000 g	22 (31.0)	19 (29.2)	5 (27.8)	6 (35.3)
1000- 1500 g	20 (28.2)	25 (38.5)	1 (5.6)	5 (29.4)
> 1500 g	29 (40.8)	21 (32.3)	12 (66.7)	6 (35.3)
Previous intubation, n (%)	26 (36.6)	27 (41.5)	6 (33.3)	6 (35.3)
Reason for intubation, n (%)				
RDS	53 (74.6)	40 (61.5)	7 (38.9)	10 (58.8)
Apnea	3 (4.2)	6 (9.2)	0 (0)	3 (17.6)
Surgery	12 (16.9)	13 (20.0)	8 (44.4)	3 (17.6)
Other	3 (4.2)	6 (9.2)	3 (16.7)	1 (5.9)
Ventilatory mode before intubation, n (%)				
Mechanical ventilation	7 (9.8)	8 (12.3)	3 (16.7)	3 (17.6)
Noninvasive ventilation	51 (71.8)	49 (75.3)	8 (44.4)	12 (70.6)
Nasal O_2, low flow	1 (1.4)	0 (0)	0 (0)	0 (0)
Room air spontaneous ventilation	10 (14.1)	6 (9.2)	5 (27.8)	2 (11.8)
Unknown	2 (2.8)	2 (3.1)	2 (11.1)	0 (0)
Median initial FiO_2 [IQR], %	50.0 [28.0;100.0]	55.0 [30.0;100.0]	36.0 [21.0;95.0]	50.0 [23.0;100.0]
Median initial SpO2, [IQR], %	98.0 [93.0;100.0]	97.0 [93.0;99.0]	98.0 [97.5;100.0]	98.0 [96.0;99.0]
First operator's previous experience, n (%)				
< 10 intubations	31 (43.7)	29 (44.6)	4 (22.2)	6 (35.3)
10 to 50 intubations	31 (43.7)	25 (38.5)	11 (61.1)	7 (41.2)
> 50 intubations	8 (11.3)	9 (13.8)	2 (11.1)	4 (23.5)
Unknown	1 (1.4)	2 (3.1)	1 (5.6)	0 (0)

Abbreviations: IQR, interquartile range; d, days; GA, gestational age; RDS, respiratory distress syndrome.

Supplemental Table 3: Primary outcome before and after the 19-month interruption

Primary outcome per study period	**Atropine +propofol group (N=89)**	**Atropine +atracurium +sufentanil group (N=82)**	**Adjusted absolute risk differences: Atropine+propofol group *minus* Atropine+atracurium+sufentanil group (95% CI)**	***P* value[a]**
Period 2012-2014	(N=71)	(N=65)		
SpO2<80% for > 60 sec, n (%)	45 (63.4)	43 (66.2)	-3.0 (-19.1 to 13.2)	.74
Period 2016	(N=18)	(N=17)		
SpO2<80% for > 60 sec, n (%)	8 (44.4)	11 (64.7)	-15.0 (-52.2 to 22.3)	.27

a: p-values were obtained from adjusted generalized mixed models