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Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study

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Background (1)

- All newborn babies, including preterms, respond to pain
- Recurring pain in neonates leads to:
  - poor cognition and motor function
  - impaired brain development and
  - altered pain responses
- Sedation and analgesia (S/A) in the NICU: Invasive and noninvasive procedures, mechanical ventilation, and medical or surgical disorders that can cause pain or stress

Background (2) and Objectives

- Concerns about neurotoxic and neuroprotective effects of analgesics (including opioids), sedatives, and anaesthetics on the developing brain.
- Very little is known, about international sedation and analgesia practices at the bedside
- Objective
  - To describe the current use of sedation, analgesia, and neuromuscular blockers at the bedside in NICUs in European countries and
  - To describe the factors associated with sedation or analgesia use

Methods: study design and participants

- EUROPAIN (EUROpean Pain Audit In Neonates): prospective cohort study, management of pain and stress with sedation and analgesia
- Survey website (www.europainsurvey.eu) Background, objectives, and methods in different languages, detailed videos, questionnaires, PowerPoint presentations, all documents and daily progress reports
- Website links: secure server (Voozanoo) for data entry into standardised questionnaires in the national language

EUROPAIN SURVEY
European survey of sedation and analgesia practices for newborns admitted to intensive care units

NeoOpioid
EUROPAIN Survey

- **Welcome**
- The NeoOpioid project
- Europain Survey Protocol
- Online Data Collection Forms
- Participating Countries
- Study Management
- Authorizations and Engagements
- Educational Material
- Publication Issues

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EUROPAIN SURVEY is on Facebook

Click here to FILL IN THE QUESTIONNAIRE (authorized users only)
Cliquez ici pour REMPLIR LE QUESTIONNAIRE (personnes autorisées)
Haga clic aquí par LLENAR EL CUESTIONARIO (personas autorizadas)
Opens in a new window / S'ouvre dans une nouvelle fenêtre / Se abre en una nueva ventana

WARNING: This is the definite questionnaire; use your center login only for TRUE PATIENTS. For tests, please use the test logins.

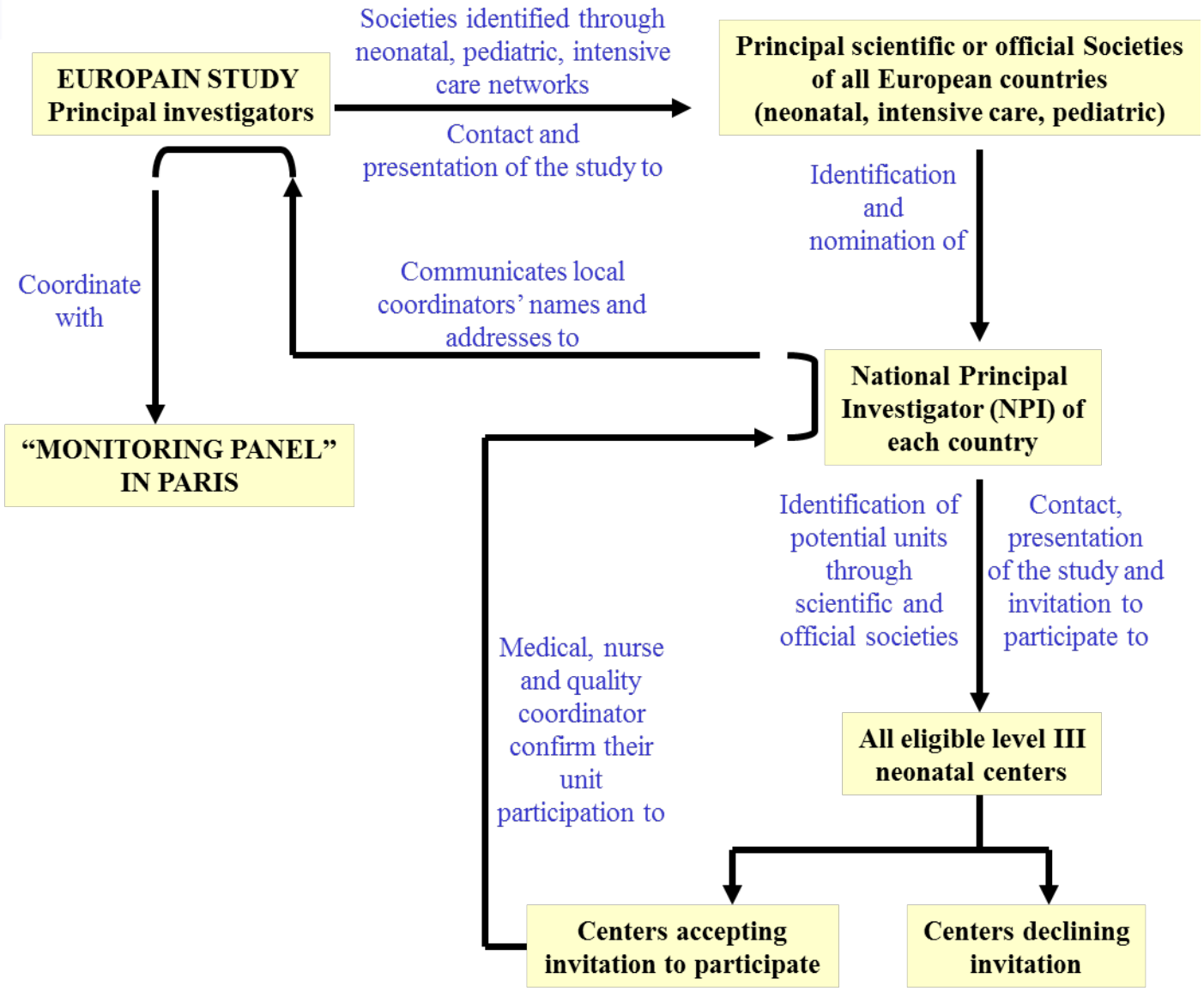
VIDEOS: some videos are available (English, French and Spanish) showing how to fill in online questionnaires

WELCOME TO THE EUROPAIN SURVEY

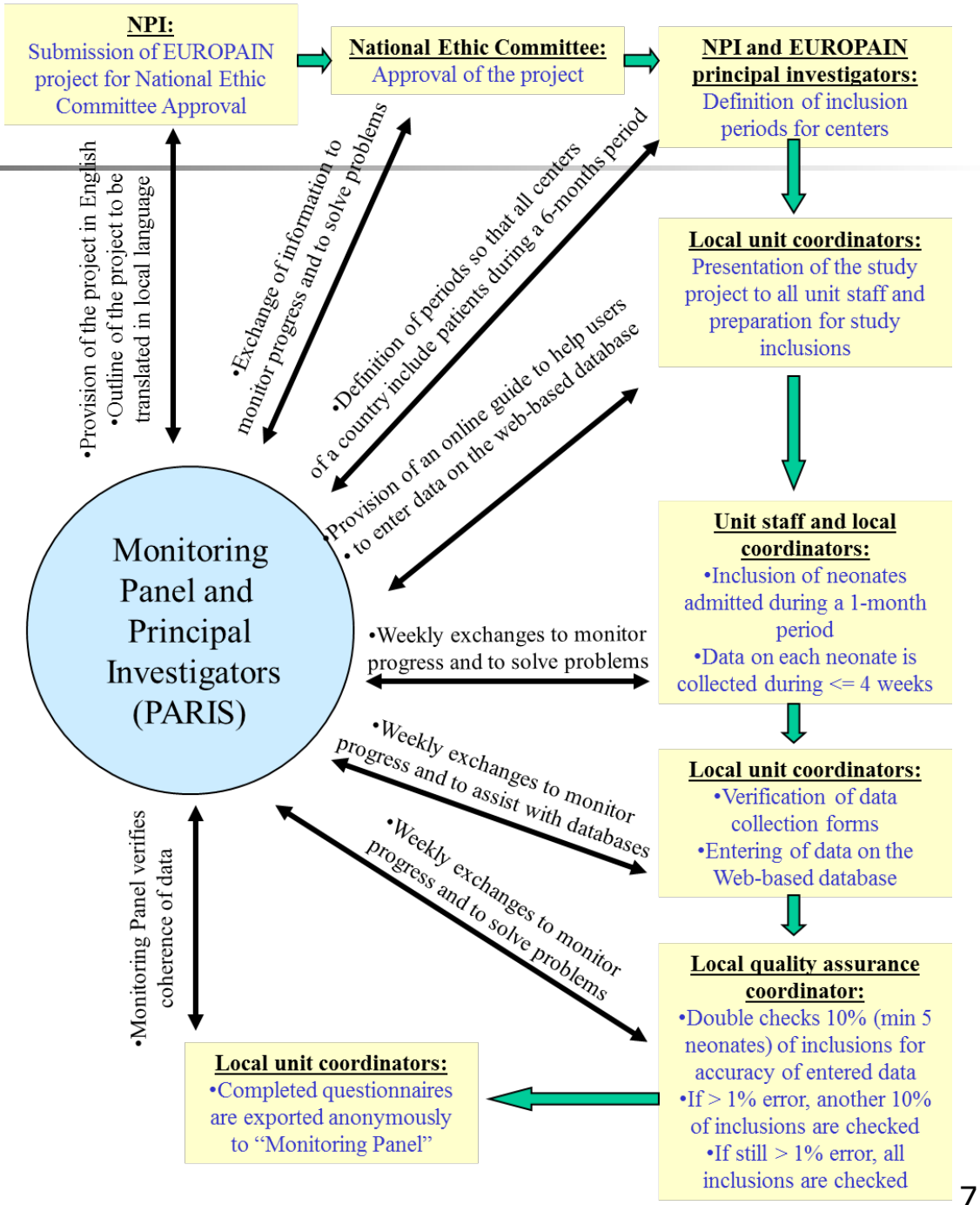
(EUROPAIN : EUROpean Pain Audit In Neonates)

The EUROPAIN SURVEY is an epidemiological study aimed at assessing current clinical practices regarding the use of sedative and analgesic drugs in newborns admitted to NICUs or PICUs in different countries in Europe.
This study is conducted as part of the **NeoOpiod Project**
This project was supported

EUROPAIN STUDY
Diagram for recruitment of centers



EUROPAIN STUDY
Sequence of main practical steps of the study



Methods: data gathering

- All neonates up to 44 weeks post-conception age
- Newly admitted
- NICUs recruited patients over 1 month
- First 28 days of stay in the hospital, or until death, discharge, or transfer:
  - demographics, methods of respiration, use of continuous or intermittent (bolus) sedation, analgesia, or neuromuscular blockers, pain assessments and specific practices to treat or prevent drug withdrawal syndromes.
- Exact durations of continuous infusion S/A

Methods: statistical analysis

- Calculated sample: 15 countries and 2300 neonates
- SPSS (v17.0) for descriptive data and Stata (v 13.0) for multivariable models and propensity score procedures
- Factors associated with S/A use, logistic regression models
- Because data were clustered, p values and 95% CIs were adjusted with a robust sandwich estimator
- Internal validation of the logistic model done with a bootstrap approach (1000 samples)

Methods: O-SH-GA and duration of tracheal ventilation

- Association between exposure to opioids, sedatives-hypnotics, or general anaesthetics (O-SH-GA) and duration of tracheal ventilation (DTV) in infants ?
- All covariates associated ($p<0{\cdot}20$) with DTV in univariate analyses were included in multivariable linear regression models
- Infants were not randomly assigned to receive O-SH-GA: propensity scores were used to reduce the effect of treatment selection bias and potential confounders

Methods: propensity score

- PS: Probability of being treated conditionally based on the individual's covariate values
- Calculated on the basis of the covariates used in the logistic regression model predicting the use of O-SH-GA
- Infants treated and not treated with O-SH-GA but with a similar propensity for treatment with O-SH-GA were matched
- Matching done with the psmatch2 algorithm in Stata, maximum calliper distance of 0·125 times the propensity score SD

Methods: propensity score and Ventilator free days

- In matched pairs, comparison of DTV in infants treated or not treated with O-SH-GA
- In all the neonates in the TV group, 2 other techniques based on the PS: stratification (comparison within quintiles), and multivariable linear regression models predicting duration of TV including the propensity score
- Ventilator free days as a secondary endpoint
  Because the rate of mortality can have an effect on the duration of TV

RESULTS

Demographics

- Oct 1, 2012, to June 30, 2013, 243 NICUs in 18 European countries enrolled 6680 neonates
- Austria, Belgium, Cyprus, Estonia, Finland, France, Germany, Greece, Italy, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Spain, Sweden, and the UK
- Six countries (33%) had national guidelines and 182 NICUs (75%) reported local protocols for neonatal S/A
- Mean gestational 35·0 weeks, birthweight was 2384 g, mean period of participation 11·9 calendar days, neonates observed for a total of 79 185 patient days

Three groups according to type of ventilation

- 3 groups on the highest level of ventilation needed:
  - Tracheal Ventilation (TV): n=2142
  - Non-invasive ventilation (NIV): n=1496
  - Spontaneous ventilation (SV): n=3042
- 2294 (34%) received S/A by continuous infusion or bolus or both: 82% in the TV group, 18% in the NIV group, and 9% in the SV group ($p<0{\cdot}0001$).
- Median use of S/A by the 243 NICUs for all neonates and for neonates in the TV group were 33·3% (IQR 18·5–56·5) and 89·3% (70·0–100), respectively

Characteristics of 3 groups

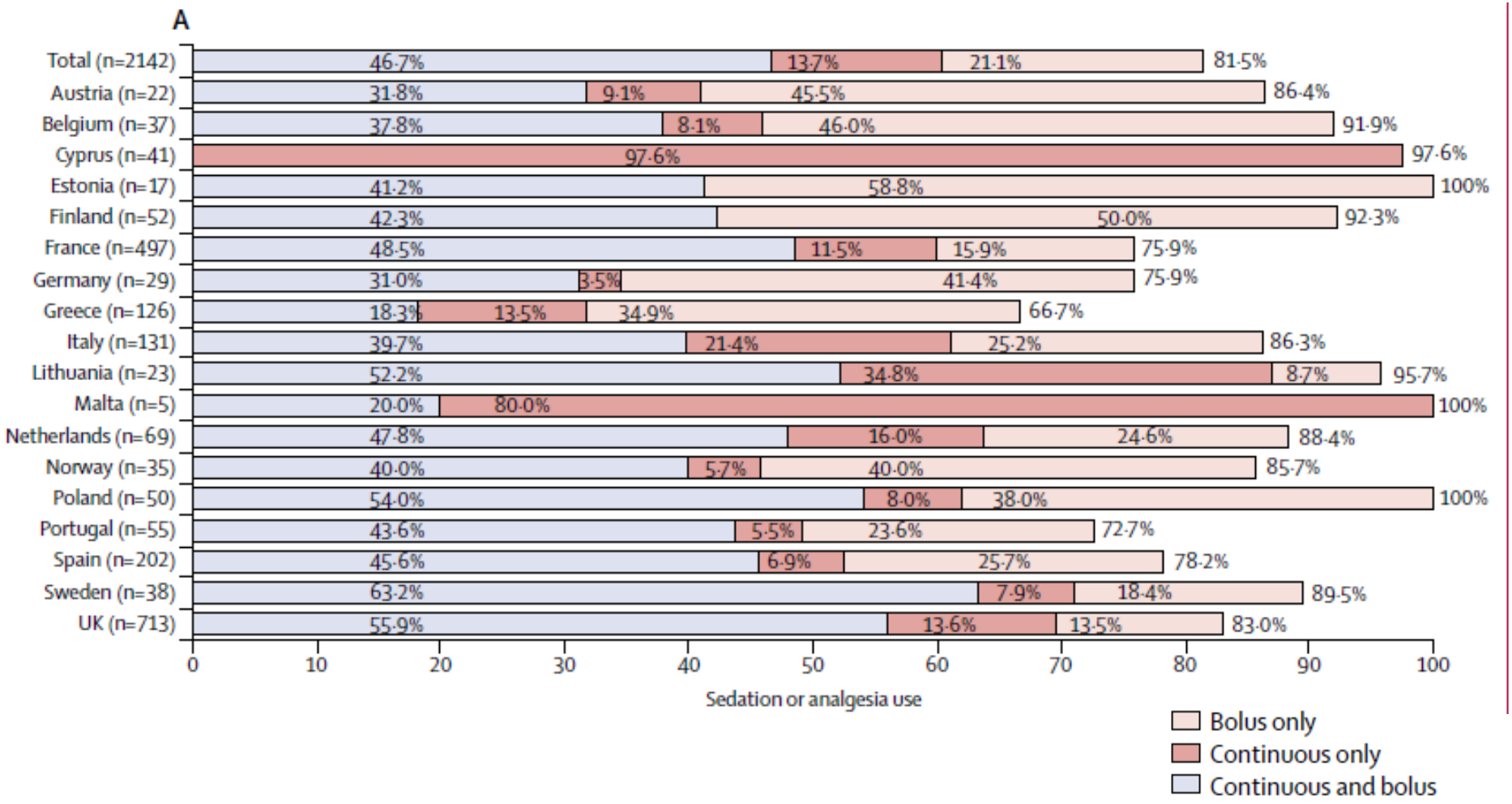
	Total (n=6680)	Tracheal ventilation (n=2142)	Non-invasive ventilation (n=1496)	Spontaneous ventilation (n=3042)	p value*
Gestational age (weeks)					
Mean (SD)	35·0 (4·6)	32·7 (5·2)	33·8 (3·8)	37·3 (3·1)	<0·0001
Median (IQR)	35·6 (32·0–39·0)	32·1 (28·1–37·4)	33·6 (31·0–36·6)	37·9 (35·0–39·9)	<0·0001
24–29	1049 (16%)	779 (36%)	214 (14%)	56 (2%)	<0·0001†
30–32	1015 (15%)	360 (17%)	454 (30%)	201 (7%)	
33–36	1864 (28%)	389 (18%)	486 (32%)	989 (33%)	
37–42	2750 (41%)	613 (29%)	342 (23%)	1795 (59%)	
Birthweight (g)					
Mean (SD)	2384 (1007)	1948 (1035)	2132 (891)	2816 (855)	<0·0001
Median (IQR)	2370 (1570–3170)	1740 (1000–2800)	1970 (1440–2720)	2870 (2140–3445)	<0·0001
Sex, male	3775 (57%)	1260 (59%)	842 (56%)	1673 (55%)	0·10
Born in same hospital as NICU	5367 (80%)	1460 (68%)	1307 (87%)	2600 (85%)	<0·0001
Type of delivery					<0·0001
Vaginal	3074 (46%)	879 (41%)	571 (38%)	1624 (53%)	
Caesarean	3586 (54%)	1249 (59%)	923 (62%)	1414 (47%)	
Age at admission (h)					
Mean (SD)	65·2 (244·3)	84·1 (294·0)	47·5 (224·2)	60·6 (212·3)	<0·0001
Median (IQR)	1·0 (0·3–12·1)	0·8 (0·3–8·3)	0·5 (0·2–1·7)	3·0 (0·4–26·8)	<0·0001
CRIB score					
Mean (SD)	1·4 (2·5)	3·3 (3·5)	0·8 (1·5)	0·4 (1·0)	<0·0001
Median (IQR)	0 (0–2)	2 (1–5)	0 (0–1)	0 (0–0)	<0·0001
Apgar score at 5 min					
Mean (SD)	8·4 (1·9)	7·4 (2·4)	8·5 (1·4)	9·0 (1·3)	<0·0001
Median (IQR)	9 (8–10)	8 (6–9)	9 (8–10)	9 (9–10)	<0·0001
Already intubated at admission	1376 (21%)‡	1376 (64%)	NA	NA	NA
Died during study	211 (3%)	201 (9%)	3 (<1%)	7 (<1%)	<0·0001
Hospital admission (days)§					
Mean (SD)	11·9 (9·7)	15·7 (10·2)	14·2 (9·9)	8·0 (7·4)	<0·0001
Median (IQR)	8 (3–20)	14 (6–28)	11 (5–26)	5 (3–11)	<0·0001

Characteristics of 3 groups and use of S/A

	Total (n=6680)	Tracheal ventilation (n=2142)	Non-invasive ventilation (n=1496)	Spontaneous ventilation (n=3042)	p value*
Sedatives or analgesics					
Method of administration					
Any form‖	2294 (34%)	1746 (82%)	266 (18%)	282 (9%)	<0·0001**
Continuous only	309 (5%)	294 (14%)	5 (<1%)	10 (<1%)	
Bolus only	937 (14%)	452 (21%)	247 (17%)	238 (8%)	
Continuous and bolus	1048 (16%)	1000 (47%)	14 (1%)	34 (1%)	
Type††					
Opioid analgesics	1764 (26%)‡‡	1589 (74%)	87 (6%)	88 (3%)	<0·0001
Sedatives-hypnotics	786 (12%)	690 (32%)	43 (3%)	53 (2%)	<0·0001
Midazolam	576 (9%)	536 (25%)	16 (1%)	24 (1%)	
Barbiturates	96 (1%)	69 (3%)	8 (1%)	19 (1%)	
Other	195 (3%)	157 (7%)	20 (1%)	18 (1%)	
General anaesthetics	199 (3%)	178 (8%)	13 (<1%)	8 (<1%)	<0·0001
Ketamine	136 (2%)	120 (6%)	9 (<1%)	7 (<1%)	
Propofol	65 (1%)	59 (3%)	5 (<1%)	1 (<1%)	
Inhalational anaesthetics	3 (<1%)	3 (<1%)	0 (0%)	0 (0%)	
Paracetamol	904 (14%)	530 (25%)	172 (11%)	202 (7%)	<0·0001
Ibuprofen	16 (<1%)	14 (1%)	1 (<1%)	1 (<1%)	<0·0001
Local anaesthetics	26 (<1%)	21 (1%)	2 (<1%)	3 (<1%)	<0·0001
Other drugs	16 (<1%)	11 (1%)	0 (0%)	5 (<1%)	0·0038
Neuromuscular blockers	542 (8%)	542 (25%)	0 (0%)	0 (0%)	<0·0001
Pain assessment with a scale§§	2838 (42%)	1250 (58%)	672 (45%)	916 (30%)	<0·0001
Withdrawal syndrome diagnosed	94 (1%)	69 (3%)	4 (<1%)	21 (1%)	<0·0001

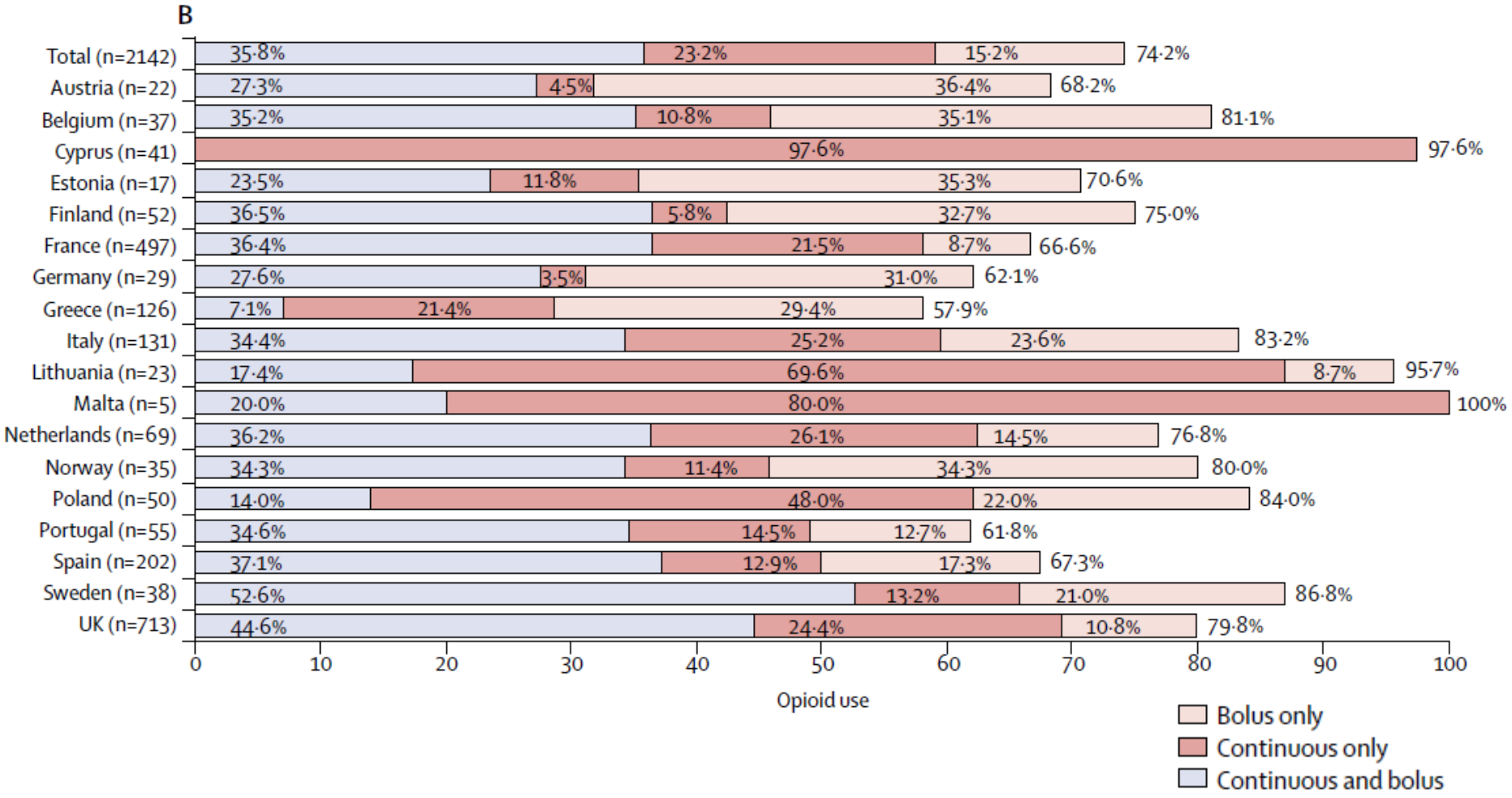
Sedation/analgesia use by country

In the TV group



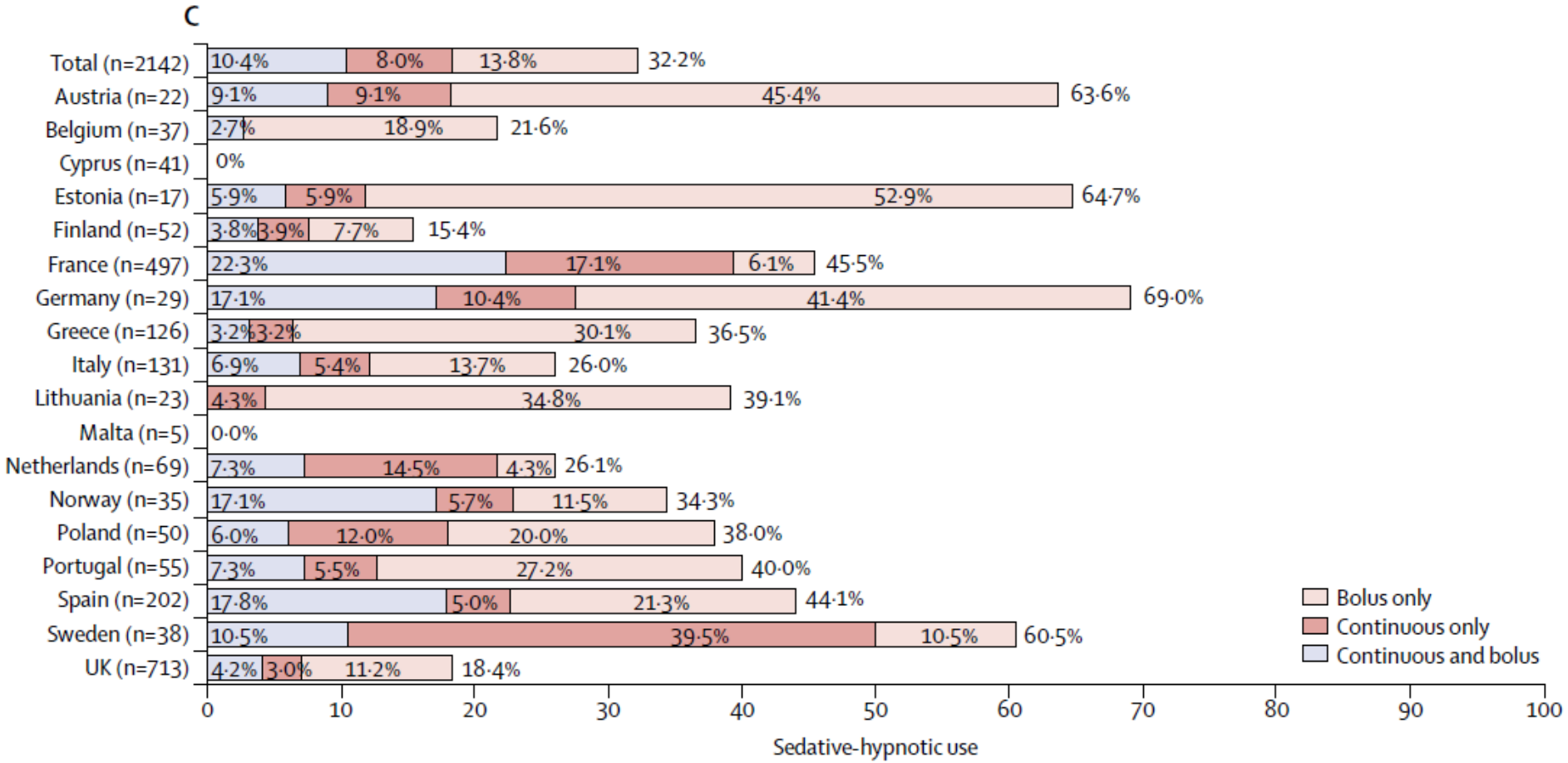
Opioid use by country

In the TV group



Sedative/Hypnotics use by country

In the TV group

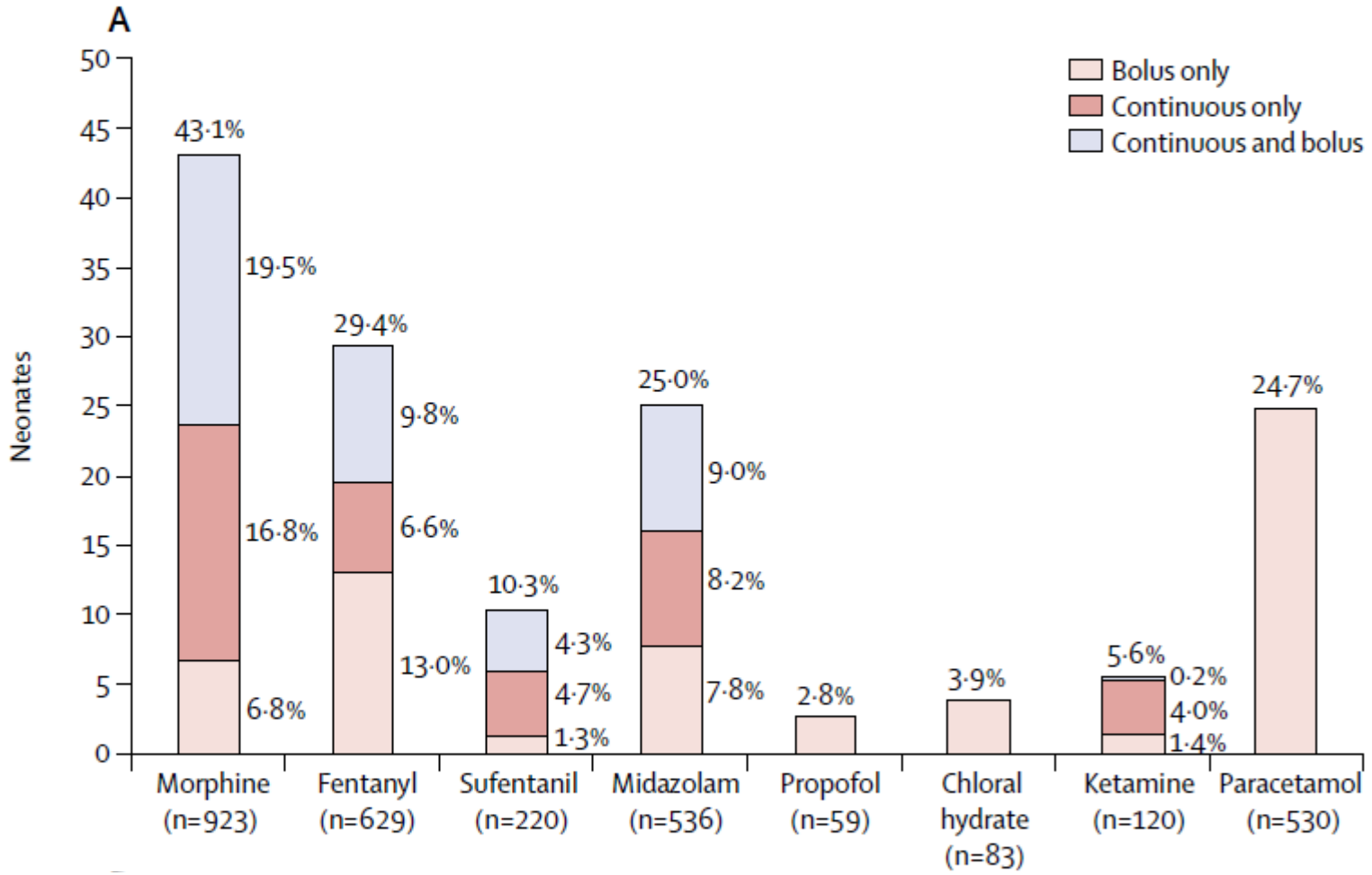


Main analgesics, sedatives-hypnotics and neuromuscular blockers, by country, in 2142 neonates who received TV

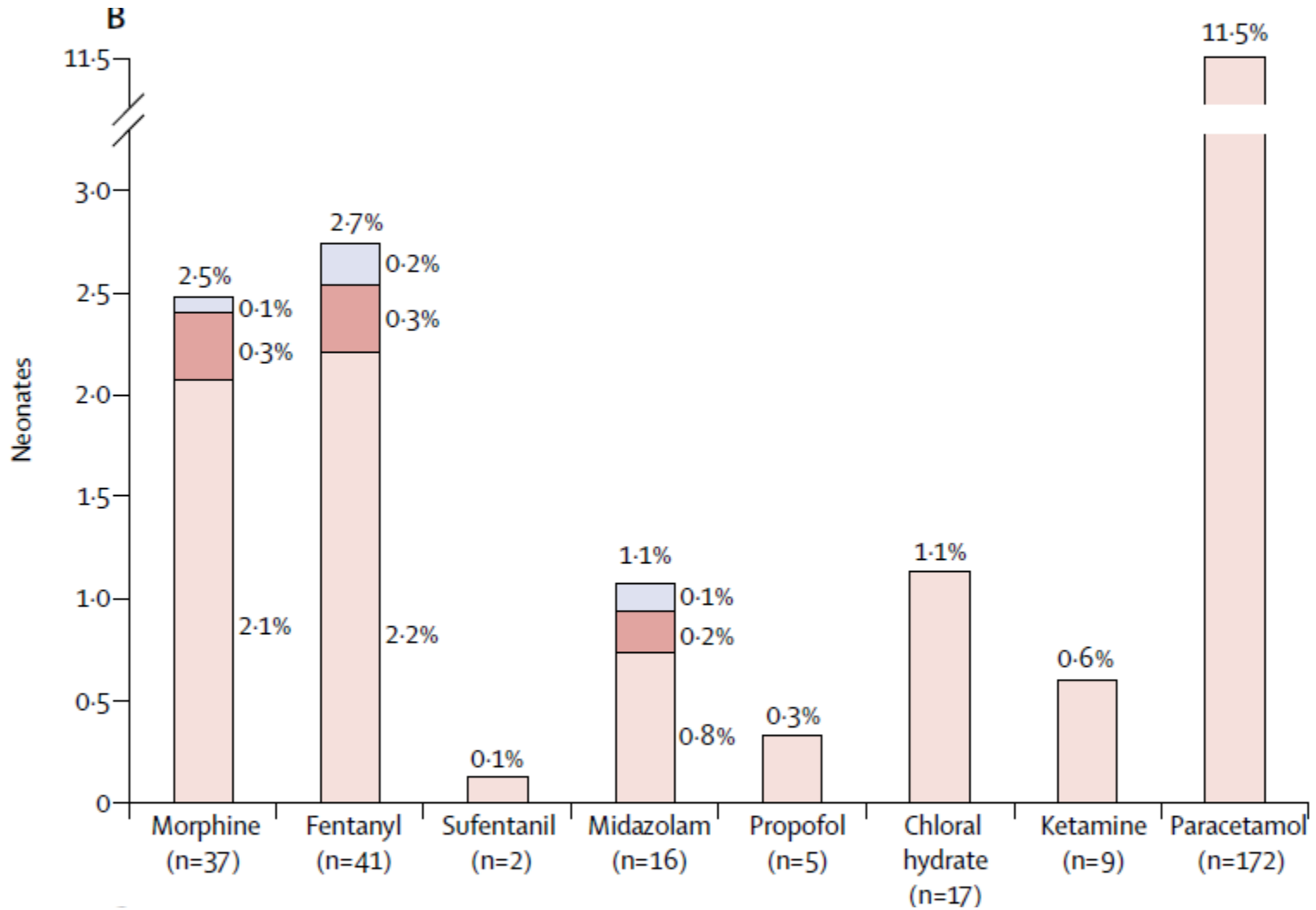
Country	Neonates with S/A n (%)	Morphine n (%)*	Fentanyl n (%)*	Sufentanil n (%)*	Ketamine n(%)*	Midazolam n (%)*	Propofol n(%)*	Chloral hydrate n (%)*	Neuromuscular blockers n (%)*	Acetaminophen n (%)*
Austria	19/22 (86.4)	5 (26.3)	12 (63.2)	-	4 (21.1)	6 (31.6)	-	5 (26.3)	3 (15.8)	7 (36.8)
Belgium	34/37 (91.9)	13 (38.2)	21 (61.8)	-	-	1 (2.9)	5 (14.7)	1 (2.9)	14 (41.2)	10 (29.4)
Cyprus	40/41 (97.6)	40 (100.0)	-	-	-	-	-	-	11 (27.5)	-
Estonia	17/17 (100.0)	1 (5.9)	12 (70.6)	-	-	10 (58.8)	-	-	1 (5.9)	8 (47.1)
Finland	48/52 (92.3)	14 (29.2)	22 (45.8)	-	6 (12.5)	8 (16.7)	2 (4.2)	-	17 (35.4)	39 (81.3)
France	377/497 (75.9)	97 (25.7)	58 (15.4)	198 (52.5)	60 (15.9)	223(44,9)	8 (2.1)	-	33 (8.8)	165 (43.8)
Germany	22/29 (75.9)	3 (13.6)	18 (81.8)	-	1 (4.5)	16 (72.7)	1 (4.5)	-	6 (27.3)	2 (9.1)
Greece	84/126 (66.7)	7 (8.3)	66 (78.6)	-	3 (3.6)	34 (40.5)	-	16 (19.0)	4 (4.8)	2 (2.4)
Italy	113/131 (86.3)	11 (9.7)	103 (91.2)	-	2 (1.8)	29 (25.7)	4 (3.5)	1 (0.9)	7 (6.2)	8 (7.1)
Lithuania	22/23 (95.7)	21 (95.5)	6 (27.3)	-	-	9 (40.9)	-	-	7 (31.8)	10 (45.5)
Malta	5/5 (100.0)	5 (100.0)	-	-	-	-	-	-	-	-
Netherlands	61/69 (88.4)	43 (70.5)	15 (24.6)	-	-	16 (26.2)	13 (21.3)	-	13 (21.3)	11 (18.0)
Norway	30/35 (85.7)	17 (56.7)	22 (73.3)	-	-	11 (36.7)	1 (3.3)	1 (3.3)	14 (46.7)	15 (50.0)
Poland	50/50 (100.0)	16 (32.0)	13 (26.0)	19 (38.0)	2 (4.0)	9 (18.0)	-	-	6 (12.0)	35 (70.0)
Portugal	40/55 (72.7)	22 (55.0)	16 (40.0)	-	-	21 (52.5)	-	2 (5.0)	4 (10.0)	16 (40.0)
Spain	158/202 (78.2)	37 (23.4)	125 (79.1)	-	5 (3.2)	76 (48.1)	7 (4.4)	1 (0.6)	45 (28.5)	47 (29.7)
Sweden	34/38 (89.5)	29 (85.3)	15 (44.1)	1 (2.9)	3 (8.8)	12 (35.3)	6 (17.6)	-	5 (14.7)	12 (35.3)
United Kingdom	592/713 (83.0)	542 (91.6)	105 (17.7)	2 (0.3)	34 (5.7)	55 (9.3)	12 (2.0)	56 (9.5)	352 (59.5)	143 (24.2)
TOTAL	1746/2142 (81.5)	923 (52.9)	629 (36.0)	220 (12.6)	120 (6.9)	536 (30.7)	59 (3.4)	83 (4.8)	542 (31.0)	530 (30.4)

*Percentages of those who received S/A
Abbreviation: S/A: Sedation/Analgesia

Frequencies and methods of administration of main medications in TV group of neonates (n=2142)



Frequencies and methods of administration of main medications in NIV group of neonates (n= 1496)



O-SH-GA use in the TV group

- 1674 (78%) were treated with O-SH-GA including 1634 (76%) who were given opioids or midazolam, or both.
- 1290 (60%) neonates in the TV group were given continuous infusions of O-SH-GA.
- 451 (21%) neonates of 2142 were given sedation or analgesia solely as boluses, including 382 (18%) who were given O-SH-GA.
  - Only 91 (4%) neonates were given four boluses or more

Factors associated with the use of O-SH-GA

- Use of S/A varied from 0% to 100% between NICUs.
- Increased use of S/A in all neonates: ventilation status, increased CRIB scores, and bedside pain assessments
- Decreased use of S/A in all neonates: preterm birth and younger age at NICU admission (<72 h)
- In the TV group, use of O-SH-GA
  Increased: CRIB scores and bedside pain assessments
  Decreased: <33 weeks of gestation, younger age (<7 h), and being already intubated at NICU admission

Logistic model of factors associated with the use of O-SH-GA in tracheally ventilated neonates (1)

	Tracheally ventilated neonates (n=2004)					
	Number of neonates	Opioids		Sedatives-hypnotics		General anaesthetics	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Sex							
Male	1180	1·00		1·00		1·00	
Female	824	0·74 (0·60–0·93)	0·008	0·91 (0·73–1·12)	0·36	1·06 (0·75–1·50)	0·74
Gestational age (weeks)							
37–42	574	1·00		1·00		1·00	
33–36	372	0·91 (0·64–1·29)	0·59	0·62 (0·46–0·83)	0·001	0·68 (0·40–1·15)	0·15
30–32	343	0·55 (0·39–0·79)	0·001	0·32 (0·23–0·46)	<0·0001	0·65 (0·37–1·13)	0·13
24–29	715	0·69 (0·49–0·99)	0·041	0·29 (0·21–0·40)	<0·0001	0·87 (0·53–1·44)	0·60
Age at admission (h)							
>168	172	1·00		1·00		1·00	
73–168	46	1·33 (0·39–4·50)	0·64	0·65 (0·33–1·28)	0·21	1·21 (0·46–3·20)	0·70
25–72	88	0·68 (0·32–1·43)	0·30	0·38 (0·22–0·65)	0·0004	0·74 (0·30–1·87)	0·53
7–24	213	0·84 (0·44–1·61)	0·60	0·48 (0·31–0·74)	0·001	0·60 (0·29–1·23)	0·16
<7	1485	0·32 (0·19–0·55)	<0·0001	0·32 (0·23–0·46)	<0·0001	0·43 (0·25–0·74)	0·002
Intrauterine growth retardation							
No	1680	1·00		1·00		1·00	
Yes	324	0·70 (0·52–0·95)	0·021	1·23 (0·94–1·61)	0·14	1·56 (1·03–2·37)	0·035

Continued…

Logistic model of factors associated with the use of O-SH-GA in tracheally ventilated neonates (2)

	Tracheally ventilated neonates (n=2004)					
	Number of neonates	Opioids		Sedatives-hypnotics		General anaesthetics	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Respiratory distress syndrome							
No	1029	1·00		1·00		1·00	
Yes	975	0·86 (0·67–1·12)	0·28	0·77 (0·60–0·98)	0·04	0·77 (0·51–1·17)	0·22
CRIB score†	2004	1·31 (1·24–1·37)	<0·0001	1·13 (1·10–1·17)	<0·0001	1·03 (0·98–1·09)	0·22
Apgar at 1 min‡	2004	1·04 (0·99–1·08)	0·09	1·04 (0·99–1·08)	0·09	0·98 (0·91–1·05)	0·60
Already intubated at admission							
No	731	1·00		1·00		1·00	
Yes	1273	0·35 (0·27–0·46)	<0·0001	0·83 (0·66–1·04)	0·11	0·30 (0·20–0·44)	<0·0001
Pain assessment with a scale							
No	848	1·00		1·00		1·00	
Yes	1156	1·73 (1·39–2·16)	<0·0001	1·80 (1·45–2·23)	<0·0001	2·63 (1·76–3·92)	<0·0001
Model area under the receiver operating characteristic curve§		0·753 (0·729–0·777)		0·731 (0·706–0·755)		0·741 (0·701–0·780)	
Optimism in apparent performance¶		–0·0000247		–0·0003018		0·0004471	
Optimism-corrected area¶		0·753 (0·729–0·777)		0·730 (0·706–0·755)		0·741 (0·701–0·781)	

Patients with missing data were not included in the logistic regression models. The p values and 95% CIs were adjusted with a robust sandwich estimator. CRIB=Clinical Risk Index for Babies. *Analysis adjusted for centres. †Odds ratio per point increase in CRIB score. ‡Odds ratio per point increase in Apgar score; this score ranges from 0 to 10. §Area with 95% CI (0·5=no predictive value; 1·0=perfect prediction). ¶An internal validation of the model was done with a bootstrap approach (1000 samples).

Linear model of factors associated with increased duration of tracheal ventilation (1)

	Univariate analysis (n=2142)			Multivariable linear model* (n=2004)		
	Number of neonates	Duration of tracheal ventilation (h; mean, SD)	p value	Number of neonates	β (SD)	p value
Sex			0·17			0·13
Male	1260	118·99 (166·62)		1180	1·00	
Female	880	109·00 (159·87)		824	−9·84 (6·49)	
Gestational age (weeks)			<0·0001			
37–42	613	76·76 (106·77)		574	1·00	
33–36	389	81·10 (115·34)		372	17·50 (9·94)	0·08
30–32	360	60·53 (99·67)		343	18·01 (10·84)	0·10
24–29	779	187·63 (213·62)		715	100·80 (9·76)	<0·0001
Age at admission (h)			0·013			
>168	224	141·75 (178·97)		172	1·00	
73–168	59	143·35 (164·62)		46	19·03 (23·74)	0·42
25–72	99	80·13 (115·31)		88	−11·91 (19·24)	0·54
7–24	231	117·50 (150·35)		213	9·60 (15·19)	0·53
<7	1529	112·02 (166·15)		1485	−11·29 (12·16)	0·35
Born in same hospital as NICU			0·81		..	
No	682	116·37 (150·87)			..	
Yes	1460	114·53 (170·15)			..	
CRIB score	2057	0·307†	<0·0001	2004	6·79 (1·08)	<0·0001
Apgar at 1 min‡	2088	−0·139†	<0·0001	2004	−2·62 (1·26)	0·037

Continued…

Linear model of factors associated with increased duration of tracheal ventilation (2)

	Univariate analysis (n=2142)			Multivariable linear model* (n=2004)		
	Number of neonates	Duration of tracheal ventilation (h; mean, SD)	p value	Number of neonates	β (SD)	p value
Intrauterine growth retardation			0·001			0·007
No	1785	109·73 (157·70)		1680	1·00	
Yes	351	141·94 (191·04)		324	23·74 (8·79)	
Respiratory distress syndrome			0·001			0·34
No	1125	103·85 (147·60)		1029	1·00	
Yes	1017	127·57 (180·09)		975	7·56 (7·89)	
Already intubated at admission			<0·0001			<0·0001
No	766	78·72 (109·89)		731	1·00	
Yes	1376	135·37 (184·73)		1273	42·22 (7·64)	
Use of opioids, sedatives-hypnotics or general anaesthetics§			<0·0001			<0·0001
No	468	39·79 (94·71)		445	1·00	
Yes	1674	136·17 (173·14)		1559	96·47 (8·36)	
Pain assessment with a scale			0·002			0·0005
No	888	101·95 (159·86)		848	1·00	
Yes	1250	123·85 (166·09)		1156	28·36 (8·11)	

Patients with missing data were not included in the multivariable linear model. The p values and 95% CIs were adjusted with a robust sandwich estimator. CRIB=Clinical Risk Index for Babies. *Also adjusted for countries. †Pearson correlation with duration of tracheal ventilation. ‡Apgar score ranges from 0 to 10. §Opioids, sedatives-hypnotics, or general anaesthetics include all opioids, ketamine, benzodiazepines, propofol, barbiturates, chloral hydrate, and other sedatives.

Duration of TV in O-SH-GA+ *vs* O-SH-GA-

- Propensity scores were calculated for 2004 (94%) infants, including 1559 (78%) who were given O-SH-GA and 445 (22%) who were not
- Propensity score matching yielded 427 pairs of infants who were or were not given O-SH-GA and eliminated previous differences in covariates
- Substantial increase in the duration of TV associated with the use of O-SH-GA
  - mean 149·0 h [SD 183·6] vs 38·2 h [88·5]
  - median 77·3 h [IQR 25·5–169·8] vs 12·5 h [5·8–28·9]; p<0·0001)

Characteristics, before and after propensity-score matching, of infants who had tracheal ventilation according to whether they received O-SH-GA

	Before matching (n=2004)				After matching (n=854)			
	Opioids and/or sedatives-hypnotics and/or general anesthetics in continuous and/or bolus				Opioids and/or sedatives-hypnotics and/or general anesthetics in continuous and/or bolus			
	Yes (n=1559)	No (n=445)	Standardized differences	P value	Yes (n=427)	No (n=427)	Standardized differences	P value
Gestational age, weeks, mean(SD)	33.0 (5.4)	32.2 (4.6)	0.142	**0.012**	31.8 (5.0)	32.3 (4.6)	-0.098	0.139
Male sex, n (%)	933 (59.9)	247 (55.5)	0.089	0.098	244 (57.1)	239 (56.0)	0.025	0.720
Birth weight, g, mean(SD)	2003 (1058)	1823 (923)	0.172	**0.002**	1794 (989)	1841 (933)	-0.056	0.402
IUGR, n (%)	261 (16.4)	63 (14.2)	0.071	0.196	65 (15.2)	60 (14.1)	0.029	0.677
CRIB Score, mean(SD) †	3.6 (3.6)	2.0 (2.6)	0.523	**<0.001**	2.3 (2.7)	2.0 (2.7)	0.096	0.101
APGAR 1 min, mean(SD)	5.7 (2.9)	5.4 (2.8)	0.108	**0.049**	5.4 (2.9)	5.4 (2.8)	-0.008	0.911
APGAR 5 min, mean(SD)	7.4 (2.4)	7.4 (2.3)	0.007	0.902	7.2 (2.5)	7.4 (2.3)	-0.092	0.190
Age at admission, hours, mean (SD)	77.5 (264.6)	30.7 (183.8)	0.228	**<0.001**	49.5 (212.7)	31.4 (187.4)	0.097	0.103
Respiratory distress syndrome, n (%)	713 (45.7)	262 (58.9)	-0.271	**<0.001**	249 (58.3)	246 (57.6)	0.010	0.885
Already intubated at admission, n (%)	916 (58.8)	357 (80.2)	-0.478	**<0.001**	327 (76.6)	339 (79.4)	-0.068	0.325
Pain assessment, n (%)	932 (59.8)	224 (50.3)	0.190	**<0.001**	228 (53.4)	224 (52.5)	0.016	0.818
Duration of mechanical ventilation, hours, mean(SD)	134.2 (172.5)	38.2 (88.6)	0.699	**<0.001**	149.0 (183.6)	38.2 (88.5)	**0.804**	**<0.001**

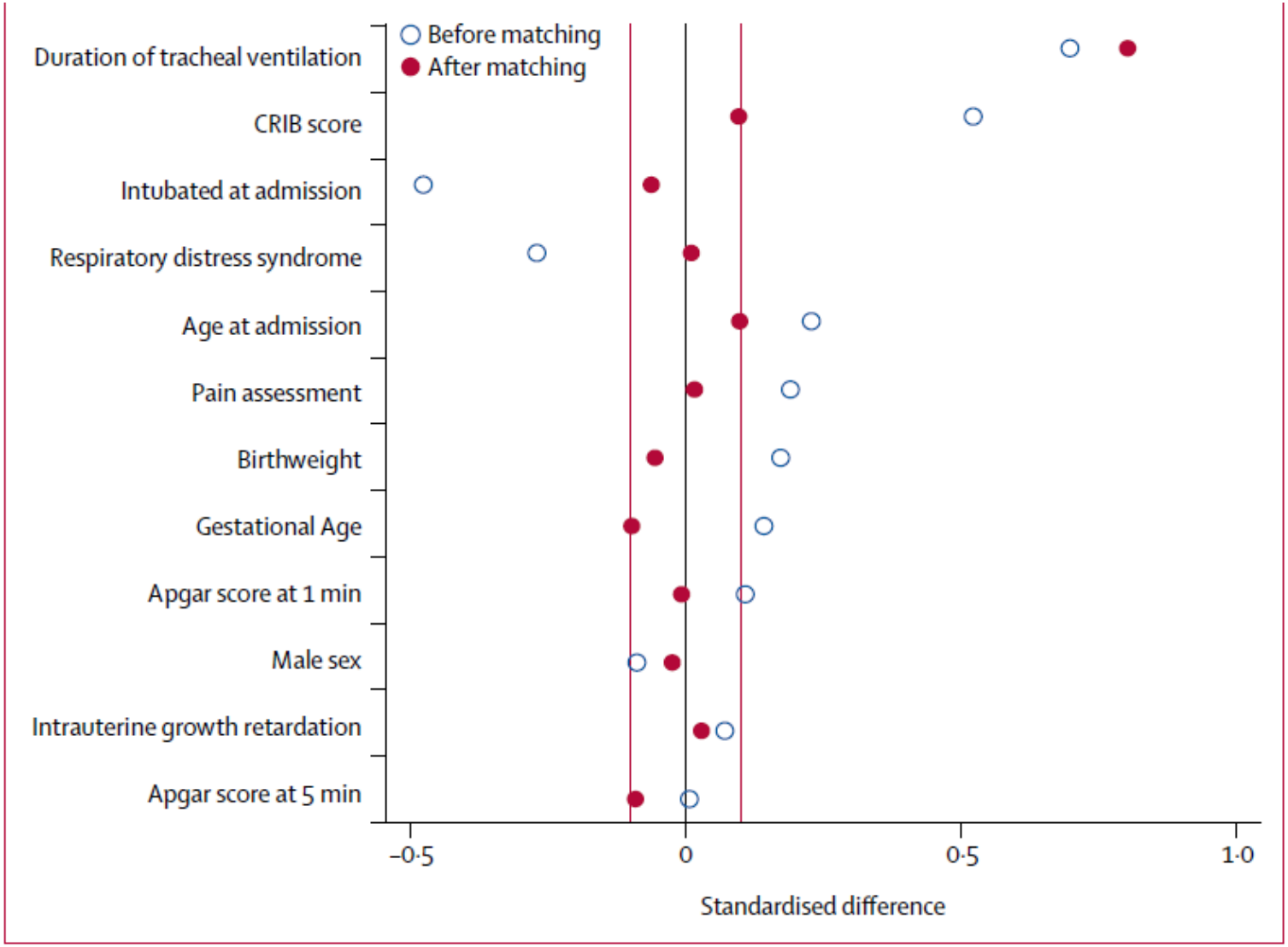
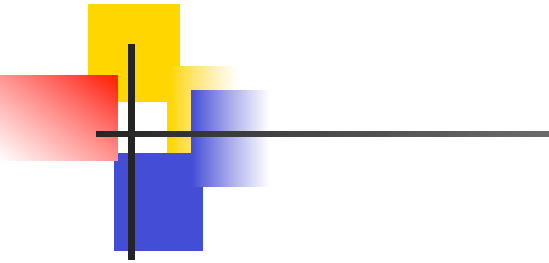


***Figure 3*: Reduction by propensity score pair matching of covariate imbalance in infants given opioids, sedatives-hypnotics, or general anaesthetics compared with those who were not**

The positions of the dots indicate the magnitude of the standardised difference between groups for each variable before and after propensity score matching (appendix). Red lines to the right and left of zero indicate the positive and negative 0·1 (10%) standardised difference limits between infants treated and not treated with opioids, sedatives-hypnotics, or general anaesthetics; standardised differences of up to 10% were judged to be inconsequential. For example, the standardised difference in CRIB score between the groups treated and not



DISCUSSION

- 34% of admissions to NICUs and 82% of neonates who were tracheally ventilated were given S/A
- In the TV group, 74% of neonates were given opioids and a quarter were given midazolam
- Wide variations between centres and countries
- S/A varied from 0% to 100% between centres
- Study cohort representative of NICU populations in Europe with the participation of 18 European countries
- Previous data: only two declarative national surveys and one cross-sectional survey

- A humane approach that includes prevention or treatment of pain in neonates is an ethical obligation
- Approach further substantiated by associations between increased pain exposure and adverse developmental outcomes
- Guidelines for procedural pain management in neonates exist whereas there are none for prolonged S/A in the NICU

- 60% of neonates in the TV group were given continuous infusions of O-SH-GA (likely given with the purpose of S/A during TV)
- O-SH-GA administered exclusively as boluses were likely given mainly for invasive procedures and less for S/A during TV
  - only 4% and 1% of neonates in the TV group were given at least four boluses and at least ten boluses

- Consistent with the results of previous studies, independent associations of sedation and analgesia with ventilation status, pain assessment, and severity of illness
- Contrary to the results of a 2010 systematic review and meta-analysis in our study exposure to O-SH-GA was associated with prolonged ventilation in the neonates

Limitations

- Participation of eligible units varied widely between countries and might not represent each country's practices
- Hawthorne effect : altered bedside practices during study enrolment
- We did not record the doses of medications used for sedation and analgesia in neonates (trade-off)
- Potential bias because neonates were classified on the basis of ever or never use of S/A
- Potential bias in the association noted between the use of O-SH-GA and longer duration of TV using the propensity score
  - PS techniques can balance baseline covariates between exposure groups, but they cannot balance unmeasured characteristics or unknown confounders

A last word

- Our findings emphasize the need
  - to develop international guidelines for the judicious use of sedation and analgesia in the NICU,
  - to investigate the therapeutic and adverse effects of these drugs in neonates, and
  - to develop new, safe approaches for sedation and analgesia in neonates

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