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Outcomes of endotracheal suctioning in non-vigorous neonates born through meconium-stained amniotic fluid: a systematic review and meta-analysis

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ABSTRACT

Objective We aimed to systematically review and analyse the outcomes of non-endotracheal suctioning (non-ETS) versus ETS in non-vigorous meconium-stained neonates.

Design We conducted a systematic review of non-ETS and ETS in non-vigorous infants born through meconium-stained amniotic fluid (MSAF). We searched PubMed/Medline, Scopus, Clinical Trials.gov, Cumulative Index to Nursing and Allied Health, and Cochrane Library databases from inception to November 2019, using keywords and related terms. Only non-vigorous infants born through MSAF included in randomised controlled trials, were included. We calculated overall relative risks (RRs) and mean differences with 95% CIs using a random-effects model, to determine the impact of ETS in non-vigorous infants born through MSAF.

Main outcome measures The primary outcome was the incidence of meconium aspiration syndrome (MAS). Secondary outcomes were respiratory outcome measures (pneumothorax, persistent pulmonary hypertension of the newborn, secondary pneumonia, need for respiratory support, duration of mechanical ventilation), initial resuscitation and others including shock, perinatal asphyxia, convulsions, neonatal mortality, blood culture-positive sepsis and duration of hospital stay.

Results A total of 2085 articles were identified in the initial database search. Four studies, including 581 non-vigorous meconium-stained infants, fulfilled the inclusion criteria, comprising 292 infants in the non-ETS group and 289 in the ETS group. No statistically significant difference was found for MAS (RR 0.98; 95% CI 0.71 to 1.35).

Conclusions Initiating ETS soon after birth in non-vigorous meconium-stained infants may not alter their neonatal outcomes.

INTRODUCTION

Meconium-stained amniotic fluid (MSAF) is a condition in which infants have passed meconium in amniotic fluid. The incidence of MSAF is generally about 5%–20% of all births^{1–3} and increases with advanced gestational age.^{4 5} MSAF can be a sign of fetal maturity or of a pathological condition, such as an infant with hypoxia.⁶ Hypoxic stress causes colonic activity leading to meconium passage and stimulating fetal gasping movements, which results in meconium aspiration.

MSAF may cause problems including meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the newborn (PPHN) and

What is already known on this topic?

- Recent data have shown that endotracheal suctioning (ETS) provides no benefit over no ETS (non-ETS) in non-vigorous meconium-stained infants.
- There is no difference in the incidence of meconium aspiration syndrome (MAS) in infants who receive ETS and those who do not.

What this study adds?

- Our results confirm that there is no difference in for many aspects of the outcomes, including MAS, between ETS versus non-ETS in non-vigorous meconium-stained infants.
- Our results support the practices in the Neonatal Resuscitation Program 2015 guideline.

hypoxic-ischaemic encephalopathy (HIE).⁷ Infants born through MSAF have a higher risk of developing respiratory distress.⁸ The incidence of MAS in meconium-stained infants is approximately 5%–10.5%, with a mortality rate of 12%. This incidence has been decreasing over time.^{9 10} Nevertheless, morbidity associated with MAS varies from mild to severe disease.^{10–13} Severe MAS carries a substantial risk of death and permanent disability.¹¹

Many strategies have been applied to reduce complications in infants born through MSAF, such as suctioning meconium from the airway. Unfortunately, studies by Wiswell *et al* did not find that the intervention of suctioning in vigorous meconium-stained infants led to a decrease in the incidence of MAS.^{14–16} Moreover, the intubation procedure may cause distress and airway injury.¹⁷ In 2000, the Neonatal Resuscitation Program (NRP) guidelines suggested mouth and pharynx suctioning of secretions before delivery of the neonate's shoulders, followed by endotracheal suctioning (ETS) only in non-vigorous infants born through MSAF.^{18 19} Since 2006, the NRP guidelines have been adjusted to mouth and tracheal suctioning under direct visualisation, without the need for mouth and pharynx suctioning at the perineum soon after birth in non-vigorous infants born through MSAF.^{20 21} Despite having been practised for a decade,²² the latest NRP 2015 guidelines no longer suggest routine ETS in non-vigorous infants delivered through MSAF.²³



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Nonetheless, the outcomes of this practice remain questionable owing to little evidence using human data.²⁴

Thus, we aimed to determine the neonatal outcomes of no ETS (non-ETS) compared with routine ETS in non-vigorous, meconium-stained infants.

Methods

We performed this systematic review and meta-analysis following the recommendations established by Preferred Reporting Items for Systematic Reviews and Meta-Analyses. We included any non-vigorous infants born through MSAF.

Outcomes

Our primary outcome was the incidence of MAS. Secondary outcomes were other respiratory outcomes (pneumothorax, PPHN, secondary pneumonia, need for respiratory support), initial resuscitation and others, including shock, perinatal asphyxia, convulsions, neonatal mortality and blood culture-positive sepsis. The durations of hospital stay and mechanical ventilation were also investigated.

Search strategy and selection criteria

A comprehensive and systematic search was performed from inception until November 2019 using PubMed/Medline, Scopus, Clinical Trials.gov, Cumulative Index to Nursing and Allied Health, and the Cochrane Library, using keywords, synonyms, and other terms related to MSAF and ETS, and with no language restrictions. Only randomised controlled trials (RCTs) and human studies were included. Additional studies were retrieved from the bibliographies of the included articles.

Two reviewers (NP and WT) independently screened the titles and/or abstracts for relevance, followed by full-text article assessment. The inclusion criteria were any non-vigorous neonates born through MSAF included in randomised clinical trials investigating the effects of non-ETS or ETS. For studies with inadequate information for meta-analysis, additional data were sought from the corresponding authors of the selected articles.

Data extraction, bias and quality assessment

Data were extracted by two reviewers (NP and WT), including study details (study design, year of publication, population and end points), patient characteristics (patient demographics, number of patients, gestational age, sex, and neonatal and maternal parameters), eligibility criteria, method of data collection, definition of outcomes and other outcomes of interest reported by the authors. To evaluate the validity of the eligible randomised trials among the included studies, two reviewers (NP and WT) independently assessed the risk of bias for each study using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2), as recommended by the Cochrane Collaboration.²⁵ Any disagreements were resolved through discussion or involvement of a third reviewer (TU).

Data analysis

Meta-analysis was performed using data for the same outcome in two or more studies. The overall relative risks (RRs) and mean differences with 95% CIs were calculated to determine the effects of ETS in non-vigorous infants born through MSAF for dichotomous outcomes and continuous outcomes, respectively. For continuous data, if the studies reported median and range or IQR, the data were converted to mean and SD.^{26,27} All analyses were carried out using the DerSimonian and Laird method in a random-effects model.²⁸ Statistical heterogeneity was assessed

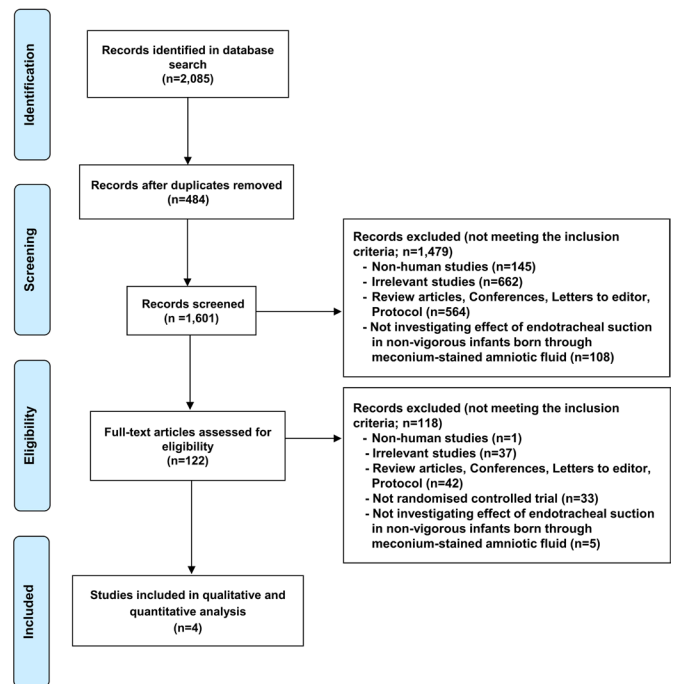


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

via the Q-statistic and I^2 tests.^{29,30} Values of $p \leq 0.05$ indicated heterogeneity between studies,²⁹ with I^2 values of 25%, 50% and 75% indicating low, moderate and high levels of heterogeneity across studies, respectively.³⁰ All statistical analyses were performed using Stata V.14.0 (StataCorp, College Station, Texas, USA).

RESULTS

Search strategy and selection criteria

Our literature search and selection criteria are summarised in figure 1. We identified 2085 articles in the initial database search. After removing duplicate records, 1601 articles were first screened on the basis of title and/or abstract, according to the inclusion criteria. Subsequently, a total 122 full-text articles were screened and 118 were further excluded for the following reasons: (1) Non-human studies (1 article). (2) Non-relevant studies (37 articles). (3) Review articles, case reports, letters to the editor, commentaries, and conference abstracts (42 articles) and non-RCTs (33 articles). (4) No investigation of the effects of ETS in non-vigorous infants born through MSAF (5 articles). Finally, four studies were included for further meta-analysis,^{31–34} with no additional articles identified in the review of bibliographies of the included studies.

Study characteristics, risk of bias and quality assessment

All investigations were conducted in various locations throughout India, and were completed before the release of the 2015 NRP guidelines. All studies were published between 2015 and 2019. The details of studies and maternal and neonatal characteristics are shown in tables 1 and 2, respectively. Outcomes were categorised according to systematic classification, including resuscitation and neonatal outcomes (table 3).

Similar definitions used in most studies and some variables were defined, as below.

1. Non-vigorous:^{31–34} heart rate < 100 beats per minute (bpm), decreased muscle tone, not breathing/crying or gasping

Table 1 Summary of the four included randomised controlled trials (RCTs)

Study	Chettri <i>et al</i> , 2015 ³¹	Nangia <i>et al</i> , 2016 ³²	Kumar <i>et al</i> , 2019 ³³	Singh <i>et al</i> , 2019 ³⁴
Type of study	RCT	RCT	RCT	RCT
Location	Pondicherry, India	New Delhi, India	Varanasi, India	Lucknow, India
Inclusion criteria	Term neonate (GA \geq 37 weeks) ▶ MSAF ▶ Non-vigorous	Term neonate (GA 37–41 weeks) ▶ Cephalic presentation ▶ Singleton ▶ MSAF ▶ Non-vigorous	Late preterm and term neonate (GA \geq 34 weeks) ▶ MSAF ▶ Non-vigorous	Late preterm and term neonate (GA \geq 34 weeks) ▶ MSAF ▶ Non-vigorous
Exclusion criteria	▶ Major congenital anomalies ▶ No consent	▶ Major congenital malformation ▶ Refusal to participate	▶ Major congenital anomalies ▶ Maternal chorioamnionitis ▶ No consent	▶ Major congenital malformation ▶ No consent
Study period	February 2013 to July 2014	May 2012 to August 2013	January 2014 to September 2015	September 2011 to August 2012
Resuscitators	One paediatric resident trained in neonatal resuscitation	Not reported	Two paediatric residents trained in neonatal resuscitation	At least two paediatric residents trained in neonatal resuscitation
Time to non-vigorous assessment	At 5–10 s after birth	At birth	At birth	At 5–10 s after birth
Procedures	Intubated with endotracheal suctioning immediately after birth	Oropharyngeal suctioning then intubated with endotracheal suctioning	Oropharyngeal suctioning then intubated with endotracheal suctioning	Intubated with endotracheal suctioning immediately after birth
Number of times endotracheal suctioning performed	Maximum of 2 times	Not reported	Generally, 2–3 times	Maximum of 2 times

GA, gestational age; MSAF, meconium-stained amniotic fluid.

- Fetal distress:^{31–34} category III fetal heart rate (absent baseline fetal heart rate tracing with recurrent late decelerations, or recurrent variable decelerations or bradycardia and sinusoidal pattern).
- Meconium consistency³¹ thin: watery-consistency fluid; moderate: opaque fluid without particles; and thick: pea-soup consistency or opaque fluid containing particulate material
- Respiratory problems:
 - MAS:^{31–34} neonates with respiratory distress of unexplained origin on chest X-ray and symptoms owing to other diseases (radiographic findings: diffuse, asymmetrical patchy infiltrates with hyperinflation, or segmental or lobular atelectasis)
 - Severity of MAS:³³ Cleary and Wiswell Score
 - Severity of respiratory distress:³² Downes Score
 - PPHN:³⁴ labile hypoxaemia (peripheral capillary oxygen saturation $<$ 90% and/or arterial partial pressure of oxygen (PaO₂) $<$ 50 mm Hg) with preductal and postductal oxygen saturation difference of $>$ 10% or PaO₂ difference of $>$ 20 mm Hg, with/without echocardiography confirmation
 - Transient tachypnoea of the newborn:³³ respiratory distress with normal or perihilar, streaky markings as radiographic features
- Perinatal asphyxia:³¹ Apgar Score \leq 6 at 5 min after birth with cord blood pH $<$ 7 and a base deficit of $>$ 12, and HIE³² as assessed by Levene's stages
- Severity of shock:³¹ Wernovsky Score.
- Obstetric problems
 - Prolonged labour:³⁴ failure to progress with labour lasting \geq 20 hours and \geq 14 hours in primiparous and multiparous women, respectively
 - Obstructed labour:³⁴ presenting part of the fetus cannot progress into the birth canal, despite strong uterine contractions
 - Premature rupture of membranes:³⁴ rupture of membranes before the onset of labour
 - Prolonged rupture of membranes:³⁴ rupture of membranes $>$ 24 hours before delivery

It should be noted that there were some concerns about risk of bias assessment based on the RoB 2 tool in all included studies (online supplementary file 1).

Study and patient characteristics

A summary of all data and patient characteristics of the included studies, which were matched between the groups, is shown in tables 1 and 2.

Outcome of the analyses

A total of 581 non-vigorous infants was recruited in this study. Of these, 292 were in the non-ETS group and 289 were in the ETS group. The evidence of heterogeneity and tests for overall effects are detailed in figure 2. In our comparison, RR $>$ 1 indicated that the risk of acquiring illness or disease was greater in the non-ETS group and RR $<$ 1 indicated that the risk of acquiring illness or disease was lower in the non-ETS group (table 3).

Outcomes of respiratory system

MAS

In four studies,^{31–34} MAS was diagnosed in 201/581 (35%) infants; non-ETS=101/292 (35%) and ETS=100/289 (35%), with no significant difference in the incidence of MAS between non-ETS and ETS groups at birth: RR 0.98; 95% CI (0.71 to 1.35).

Other respiratory outcomes, such as pneumothorax, PPHN and secondary pneumonia were not indicated as statistically significant effects of ETS at birth. Results regarding the need for respiratory support, including mechanical ventilation or even mechanical ventilation alone, were similar. Kumar *et al*³³ also reported results for pulmonary haemorrhage.

Outcomes of other systems, including cardiovascular system, neurological system infection and neonatal mortality

The overall outcomes with respect to other systems exhibited that non-ETS would not result in a higher risk of these complications. Cardiovascular problems, such as shock, neurological outcomes like perinatal asphyxia/HIE or convulsions, were not significantly different, as compared with the other group.

Table 2 Maternal and neonatal characteristics

Characteristics	Chettri <i>et al</i> , 2015 ³¹		Nangia <i>et al</i> , 2016 ³²		Kumar <i>et al</i> , 2019 ³³		Singh <i>et al</i> , 2019 ³⁴	
	Non-ETS=61	ETS=61	Non-ETS=88	ETS=87	Non-ETS=66	ETS=66	Non-ETS=77	ETS=75
Maternal age (years), mean±SD	25.2±4.8	24.3±4.5	NR		25.2±4.0	26.4±4.5	26.6±3.7	27.1±3.6
Mode of delivery								
SVD, n (%)	9 (15)	13 (21)	NR		17 (26)	8 (12)	18 (23)	26 (35)
Caesarean/low segment C-section, n (%)	30 (49)	29 (48)	37 (42)	34 (39)	49 (74)	57 (86)	30 (39)	30 (40)
Gravida								
Gravida (<2nd gravida), n (%)	NR		66 (75)	65 (75)	NR		NR	
Multigravida, n (%)	NR		NR		NR		38 (49)	33 (44)
Antenatal care								
Antenatally registered, n (%)	NR		49 (56)	58 (67)	NR		NR	
Antenatal care (≥3 visits), n (%)	NR		NR		23 (35)	24 (36)	NR	
Antenatal care (≥4 visits), n (%)	NR		NR		NR		57 (74)	49 (65)
Maternal risk factors								
Maternal risk factors I anaemia; Hb <10.5 g/dL, n (%) ([#] Hb <10 g/dL)	18 (30)	17 (28)	NR		NR		9 (12) [#]	12 (16) [#]
Maternal risk factors II (PIH, pre-eclampsia, eclampsia), n (%)	6 (10)	9 (15)	Included in other risk factors		15 (23)	13 (20)	19 (25)	23 (31)
Other maternal risk factors III (^λ PIH, HT, GDM, renal diseases/ oligohydramnios/ cardiovascular disease), n (%)	3 (5) ^{††}	3 (5) ^{††}	15 (17) ^λ	22 (25) ^λ	NR		3 (4) ^{††}	2 (3) ^{††}
^{††} GDM on insulin, hypothyroid, rheumatic heart disease								
Oligohydramnios, n (%)	6 (10)	8 (13)	NR		6 (9)	7 (11)	1 (1)	2 (3)
Premature rupture of membranes, n (%)	10 (16)	11 (18)	NR		NR		23 (30)	19 (25)
Prolonged rupture of membranes, n (%)	NR		NR		NR		13 (17)	13 (17)
Thick meconium, n (%)	39 (64)	42 (69)	69 (78)	61 (70)	30 (45)	28 (42)	47 (61)	47 (63)
Neonatal characteristics								
Male, n (%)	36 (59)	33 (54)	52 (59)	52 (60)	29 (44)	35 (53)	43 (56)	40 (53)
Birth weight (g), mean±SD	2900±350	2870±490	2763±533	2649±437	2528±598	2620±696	2461±192	2462±315
Gestational age (weeks) median (IQR)	37–41 ^{6/7} weeks	37–41 ^{6/7} weeks	39 (37–40)	39 (37–40)	38 (36–40)	38 (36–40)	38.56±2.0	38.57±2.2
[#] Chettri <i>et al</i> , 2015 n (%)	57 (93) [#]	41 ^{6/7} weeks						
	≥42 weeks	55 (90) [#]						
	4 (7) [#]	≥42 weeks						
		6 (10) [#]						
Apgar Score at 1 min ≤3, n (%)	36 (59)	37 (61)	22 (25)	18 (21)	27 (41)	33 (50)	25 (32)	29 (39)
Apgar Score at 5 min ≤3, n (%)	2 (3)	2 (3)	NR	NR	4 (6)	3 (5)	0 (0)	1 (1)
Apgar Score at 5 min <7, n (%)	27 (44)	30 (49)	13 (15)	16 (18)	15 (23)	13 (20)	26 (34)	30 (40)
Cord blood pH	6.90±0.32	6.92±0.36	7.14±0.13	7.13±0.14	NR	NR	7.09±0.11	7.08±0.11
Cord blood base deficit	14±6.28	15±7.84	8.23±6.19	8.06±5.78	NR	NR	15.77±3.13	15.86±3.22

All values are reported as frequency (%), unless otherwise noted.

ETS, endotracheal suctioning; GDM, gestational diabetes mellitus; Hb, haemoglobin; HT, hypertension; Non-ETS, no endotracheal suctioning; NR, not reported; PIH, pregnancy-induced hypertension; SD, standard deviation; SVD, normal spontaneous vaginal delivery.

Chettri *et al*³¹ reported the results of mental and motor development delay according to the Differential Ability Scales, Second Edition for Indian infants whereas intracranial haemorrhage was demonstrated in the study by Kumar *et al*.³³

Both neonatal mortality and blood culture-positive sepsis were demonstrated in the same direction. ETS did not affect these outcomes.

Kumar *et al*³³ also reported the results of gastrointestinal bleeding, acute kidney injury, thrombocytopenia, abnormal glucose level and electrolyte imbalance.

Outcomes regarding the need for initial resuscitation

Positive pressure ventilation, chest compression and epinephrine use during resuscitation were not different between groups. On the whole, the results in the non-ETS group were not significantly different for initial resuscitation needed over the ETS group.

Duration of mechanical ventilation (hours) and hospital stay (days)

Both durations of mechanical ventilation and hospital stay were not decreased with ETS at birth.

DISCUSSION

This was a systematic review and meta-analysis regarding non-ETS and ETS in meconium-stained infants, following release of NRP 2015. Our study comprised four RCTs between 2011 and 2015 conducted in different parts of India according to the NRP 2010 guideline. These four RCTs were published between 2015 and 2020, to provide further information and precisely determine whether non-ETS or ETS could benefit these infants. In total, 581 non-vigorous meconium-stained infants were eligible for the study and were classified as belonging to either the non-ETS (292 infants) or ETS (289 infants) groups. Our systematic

Table 3 Outcomes by system

	Non-ETS (n)		ETS (n)		RR (95% CI)
	Yes	No	Yes	No	
Outcomes of respiratory system					
Meconium aspiration syndrome					
Chettri <i>et al</i> , 2015 ³¹	19	42	20	41	0.95 (0.57 to 1.59)
Nangia <i>et al</i> , 2016 ³²	23	65	28	59	0.81 (0.51 to 1.29)
Kumar <i>et al</i> , 2019 ³³	15	51	21	45	0.71 (0.40 to 1.26)
Singh <i>et al</i> , 2019 ³⁴	44	33	31	44	1.38 (0.99 to 1.93)
Subtotal ($I^2=48.5\%$, $p=0.12$)					0.98 (0.71 to 1.35)
Total events/total infants (%)	101/292 (35)		100/289 (35)		201/581 (35)
Pneumothorax					
Chettri <i>et al</i> 2015 ³¹	1	60	1	60	1.00 (0.06 to 15.63)
Nangia <i>et al</i> 2016 ³²	2	86	2	85	0.99 (0.14 to 6.86)
Singh <i>et al</i> 2019 ³⁴	2	75	3	72	0.65 (0.11 to 3.78)
Subtotal ($I^2=0.0\%$, $p=0.94$)					0.82 (0.25 to 2.66)
Total events/total infants (%)	5/226 (2)		6/223 (3)		11/449 (2)
Persistent pulmonary hypertension of the newborn					
Chettri <i>et al</i> 2015 ³¹	2	59	4	57	0.50 (0.10 to 2.63)
Kumar <i>et al</i> 2019 ³³	2	64	4	62	0.50 (0.09 to 2.64)
Singh <i>et al</i> 2019 ³⁴	7	70	6	69	1.14 (0.40 to 3.22)
Subtotal ($I^2=0.0\%$, $p=0.59$)					0.79 (0.36 to 1.73)
Total events/total infants (%)	11/204 (5)		14/202 (7)		25/406 (6)
Secondary pneumonia					
Chettri <i>et al</i> 2015 ³¹	8	53	6	55	1.33 (0.49 to 3.61)
Singh <i>et al</i> 2019 ³⁴	19	58	17	58	1.09 (0.61 to 1.93)
Subtotal ($I^2=0.0\%$, $p=0.73$)					1.14 (0.70 to 1.88)
Total events/total infants (%)	27/138 (20)		23/136 (17)		50/274 (18)
Need for respiratory support, including mechanical ventilation					
Nangia <i>et al</i> , 2016 ³²	15	73	17	70	0.87 (0.47 to 1.63)
Kumar <i>et al</i> , 2019 ³³	47	19	48	18	0.98 (0.79 to 1.21)
Singh <i>et al</i> , 2019 ³⁴	69	8	65	10	1.03 (0.92 to 1.16)
Subtotal ($I^2=0.0\%$, $p=0.73$)					1.02 (0.92 to 1.13)
Total events/total infants (%)	131/231 (57)		130/228 (57)		261/459 (57)
Need for mechanical ventilation					
Chettri <i>et al</i> , 2015 ³¹	15	46	14	47	1.07 (0.57 to 2.02)
Nangia <i>et al</i> , 2016 ³²	8	80	11	76	0.72 (0.30 to 1.70)
Kumar <i>et al</i> , 2019 ³³	8	58	9	57	0.89 (0.37 to 2.16)
Singh <i>et al</i> , 2019 ³⁴	13	64	11	64	1.15 (0.55 to 2.41)
Subtotal ($I^2=0.0\%$, $p=0.85$)					0.98 (0.67 to 1.43)
Total events/total infants (%)	44/292 (15)		45/289 (16)		89/581 (15)
Outcomes of cardiovascular system, neurological system, neonatal mortality and infection					
Outcomes of cardiovascular system					
Shock					
Chettri <i>et al</i> , 2015 ³¹	15	46	12	49	1.25 (0.64 to 2.45)
Kumar <i>et al</i> , 2019 ³³	4	62	9	57	0.44 (0.14 to 1.37)
Subtotal ($I^2=58.7\%$, $p=0.12$)					0.83 (0.30 to 2.24)
Total events/total infants (%)	19/127 (15)		21/127 (17)		40/254 (16)
Outcomes of nervous system					
Perinatal asphyxia/hypoxic-ischaemic encephalopathy					
Chettri <i>et al</i> , 2015 ³¹	17	44	19	42	0.89 (0.52 to 1.55)
Nangia <i>et al</i> , 2016 ³²	27	61	28	59	0.95 (0.62 to 1.48)
Kumar <i>et al</i> , 2019 ³³	10	56	8	58	1.25 (0.53 to 2.97)
Singh <i>et al</i> , 2019 ³⁴	30	47	20	55	1.46 (0.91 to 2.33)
Subtotal ($I^2=0.0\%$, $p=0.48$)					1.10 (0.85 to 1.43)
Total events/total infants (%)	84/292 (29)		75/289 (26)		159/581 (27)
Convulsions					
Chettri <i>et al</i> , 2015 ³¹	23	38	23	38	1.00 (0.63 to 1.58)
Kumar <i>et al</i> , 2019 ³³	5	61	6	60	0.83 (0.27 to 2.60)
Subtotal ($I^2=0.0\%$, $p=0.77$)					0.98 (0.64 to 1.49)
Total events/total infants (%)	28/127 (22)		29/127 (23)		57/254 (22)
Neonatal mortality					

Continued

Table 3 Continued

	Non-ETS (n)		ETS (n)		RR (95% CI)
	Yes	No	Yes	No	
Chettri <i>et al</i> , 2015 ³¹ (in 7 days)	8	53	7	54	1.14 (0.44 to 2.96)
Nangia <i>et al</i> , 2016 ³²	4	84	9	78	0.44 (0.14 to 1.37)
Kumar <i>et al</i> , 2019 ³³	5	61	9	57	0.56 (0.20 to 1.57)
Singh <i>et al</i> , 2019 ³⁴	7	70	4	71	1.70 (0.52 to 5.58)
Subtotal ($I^2=17.1%$, $p=0.31$)					0.83 (0.46, 1.49)
Total events/total infants (%)	24/292 (8)		29/289 (10)		53/581 (9)
Outcomes of infection					
Blood culture-positive sepsis					
Chettri <i>et al</i> , 2015 ³¹	5	56	3	58	1.67 (0.42 to 6.67)
Kumar <i>et al</i> , 2019 ³³	0	66	2	64	0.20 (0.01 to 4.09)
Singh <i>et al</i> , 2019 ³⁴	1	76	3	72	0.32 (0.03 to 3.05)
Subtotal ($I^2=21.2%$, $p=0.28$)					0.74 (0.20 to 2.76)
Total events/total infants (%)	6/204 (3)		8/202 (4)		14/406 (3)
Outcomes regarding the need for initial resuscitation					
Positive pressure ventilation					
Chettri <i>et al</i> , 2015 ³¹	55	6	53	8	1.04 (0.91 to 1.18)
Nangia <i>et al</i> , 2016 ³²	79	9	68	19	1.15 (1.01 to 1.31)
Kumar <i>et al</i> , 2019 ³³	37	29	41	25	0.90 (0.68 to 1.20)
Singh <i>et al</i> , 2019 ³⁴	56	21	53	22	1.03 (0.84 to 1.26)
Subtotal ($I^2=1.1%$, $p=0.39$)					1.06 (0.98 to 1.15)
Total events/total infants (%)	227/292 (78)		215/289 (74)		442/581 (76)
Positive pressure ventilation via ET tube					
Chettri <i>et al</i> , 2015 ³¹	27	34	31	30	0.87 (0.60 to 1.27)
Nangia <i>et al</i> , 2016 ³²	14	74	16	71	0.87 (0.45 to 1.66)
Kumar <i>et al</i> , 2019 ³³	25	41	31	35	0.81 (0.54 to 1.20)
Singh <i>et al</i> , 2019 ³⁴	23	54	20	55	1.12 (0.67 to 1.86)
Subtotal ($I^2=0.0%$, $p=0.79$)					0.89 (0.71 to 1.12)
Total events/total infants (%)	89/292 (30)		98/289 (34)		187/581 (32)
Chest compression					
Chettri <i>et al</i> , 2015 ³¹	1	60	3	58	0.33 (0.04 to 3.12)
Nangia <i>et al</i> , 2016 ³²	2	86	1	86	1.98 (0.18 to 21.41)
Kumar <i>et al</i> , 2019 ³³	5	61	3	63	1.67 (0.42 to 6.69)
Singh <i>et al</i> , 2019 ³⁴	4	73	4	71	0.97 (0.25 to 3.75)
Subtotal ($I^2=0.0%$, $p=0.64$)					1.11 (0.48 to 2.55)
Total events/total infants (%)	12/292 (4)		11/289 (4)		23/581 (4)
Epinephrine					
Chettri <i>et al</i> , 2015 ³¹	1	60	3	58	0.33 (0.04 to 3.12)
Nangia <i>et al</i> , 2016 ³²	1	87	1	86	0.99 (0.06 to 15.56)
Kumar <i>et al</i> , 2019 ³³	2	64	1	65	2.0 (0.19 to 21.53)
Singh <i>et al</i> , 2019 ³⁴	1	76	1	74	0.97 (0.06 to 15.29)
Subtotal ($I^2=0.0%$, $p=0.75$)					0.85 (0.24 to 2.97)
Total events/total infants (%)	5/292 (2)		6/289 (2)		11/581 (2)
Duration of mechanical ventilation and hospital stay*					
Duration of mechanical ventilation (h)					Mean difference (95% CI)
Nangia <i>et al</i> , 2016 ³²	31.5±10.50		30±10.00		1.50 (-1.54 to 4.54)
Kumar <i>et al</i> , 2019 ³³	24±40.74		34±34.07		-10.00 (-22.81 to 2.81)
Singh <i>et al</i> , 2019 ³⁴	83.04±15.84		78.48±26.40		4.56 (-2.38 to 11.50)
Subtotal ($I^2=47.9%$, $p=0.15$)					0.90 (-4.37 to 6.17)
Duration of hospital stay (d)					Mean difference (95% CI)
Nangia <i>et al</i> , 2016 ³²	2.95±0.86		2.99±1.26		-0.04 (-0.36 to 0.28)
Kumar <i>et al</i> , 2019 ³³	1.83±2.35		2.25±3.40		-0.42 (-1.42 to 0.58)
Singh <i>et al</i> , 2019 ³⁴	11.17±3.73		9.91±3.06		1.26 (0.18 to 2.34)
Subtotal ($I^2=66.2%$, $p=0.05$)					0.19 (-0.59 to 0.97)

RR >1 indicated that the risk of acquiring illness or disease was greater in the non-ETS group and RR <1 indicated that the risk of acquiring illness or disease was lower in the non-ETS group

*The data were converted from median and range or IQR to mean and SD.

CI, confidence interval; ETS, endotracheal suctioning; RR, relative risk.

review and meta-analysis yielded no increasing incidence of MAS, which was the primary outcome. Overall, our study showed that neonatal outcomes with respect to respiratory, cardiovascular

and neurological systems; neonatal mortality; blood culture-positive sepsis; and the need for initial resuscitation; including the durations of mechanical ventilation and hospital stay, were

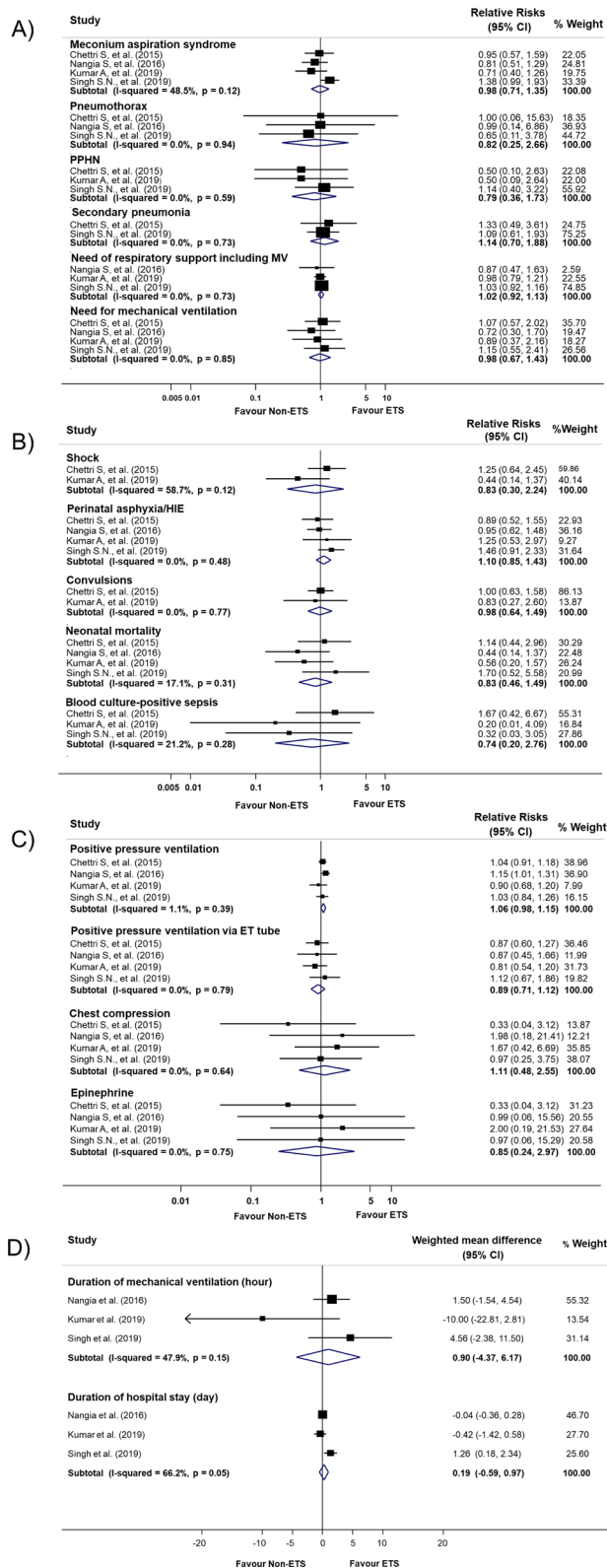


Figure 2 Forest plots of meta-analysis for neonatal outcomes of non-endotracheal suctioning compared with endotracheal suctioning in non-vigorous neonates born through meconium-stained amniotic fluid. (A) Outcomes of respiratory system. (B) Outcomes of cardiovascular system, nervous system, neonatal mortality and infection. (C) Outcomes regarding the need for initial resuscitation. (D) Duration of mechanical ventilation and hospital stay. ETS, endotracheal suctioning; HIE, hypoxic-ischaemic encephalopathy; PPHN, persistent pulmonary hypertension of the newborn; MV, mechanical ventilation

comparable between the non-ETS and ETS groups. Therefore, our systematic review and meta-analysis supported the use of the NRP 2015 guidelines for non-routine ETS in non-vigorous infants born through MSAF.

Recently, Chiruvolu *et al*³⁵ revealed an increase in neonatal intensive care unit admission for respiratory problems, mechanical ventilation, oxygen use and surfactant therapy in non-vigorous, meconium-stained infants using the latest NRP. The limitation of observational study design with uncontrollable confounding variables in this study may contribute to the distinction.

The inclusion of RCTs was the strength of this study, though some limitations remain. First, differences were noted in details of the included studies, such as time to non-vigorous assessment, oropharyngeal suctioning before ETS, with a possible indirect infant stimulation and the diversity of non-vigorous infant's clinical characters, which may have an impact on the outcomes. Chettri *et al*³¹ and Singh *et al*³⁴ assessed infants as vigorous or non-vigorous within 5–10s of birth. Whereas, Nangia *et al*³² evaluated infants immediately at birth, similarly to Kumar *et al*.³³ Oropharyngeal suctioning was performed before ETS in two studies.^{32,33} Furthermore, the proportion of neonates who had Apgar Score <7 at 5 min or acidemia (cord blood pH ≤7.2) was high in some studies,^{31,34} which may represent potentially sicker non-vigorous neonates. Second, there were insufficient data on the complications of intubation. Lastly, the interventions in all studies were undertaken by one or two trained providers in each centre, based in India. Thus, the findings may not be generalisable to other healthcare settings or more experienced providers.

Importantly, one of the most worrisome factors among paediatricians regarding the practice of ETS in non-vigorous meconium-stained infants is the delayed resuscitation because neonates may lose the opportunity to undergo a timely and effective resuscitation process. Although ETS is not routinely administered in non-vigorous meconium-stained neonates according to the NRP 2015 guidelines, if meconium blockage is suspected, resuscitators can perform ETS with a meconium aspirator.²³

According to the aforementioned data, the lack of comprehensive data may contribute to higher heterogeneity in some aspects of the results. A large, appropriately powered and designed RCT should be further established to determine the best practice for non-vigorous meconium-stained neonates.

While working on our study, Trevisanuto *et al* reported on the tracheal suctioning of meconium at birth for non-vigorous infants; their findings demonstrated insufficient evidence to suggest immediate routine direct laryngoscopy for tracheal suctioning,³⁶ of which the results were concordant with our study.

In conclusion, our systematic review and meta-analysis of RCTs on the resuscitation of non-vigorous meconium-stained infants yielded no difference in the outcomes of neonates receiving or not receiving ETS.

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