

Assessment of Change in Practice to Routine Tracheal Suctioning Approach of Non-Vigorous Infants Born Through Meconium-Stained Amniotic Fluid – A Pragmatic Systematic Review and Meta-Analysis of Evidence Outside Randomized Trials

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31 ABSTRACT

32 **Aim:** The 2015 recommendation of the International Liaison Committee on Resuscitation of
 33 no routine tracheal suctioning in non-vigorous neonates born through meconium stained
 34 amniotic fluid (MSAF) was based on very low certainty of evidence (CoE) necessitating
 35 ongoing monitoring. The aim of this systematic review was to perform a meta-analysis of
 36 observational studies comparing the effect of implementing immediate resuscitation without
 37 routine tracheal suctioning versus routine suctioning in neonates born through MSAF

38 **Methods:** Medline, Embase, CENTRAL, Web of Science were searched. Observational
 39 studies with a before and after design were included. Two authors extracted data
 40 independently. CoE based on GRADE recommendations was performed.

41 **Results:** 13 studies were included. Clinical benefit or harm could not be excluded for the
 42 composite primary outcome of mortality or requirement of extracorporeal membranous
 43 oxygenation (ECMO) [Relative risk (RR), 95% confidence interval (CI): 0.74 (0.47 to 1.17)]
 44 and mortality [0.68 (0.42 to 1.11)]. 'Routine tracheal suctioning' epoch had possibly lesser
 45 risk of meconium aspiration syndrome (MAS) when compared to 'no routine tracheal
 46 suctioning' epoch [0.68 (0.47 to 0.99)]. 'Routine tracheal suctioning' epoch also possibly had
 47 a lower risk of hospital admission for respiratory symptoms, requirement of non-invasive
 48 respiratory support, invasive mechanical ventilation, surfactant treatment, air-leak and low-
 49 flow oxygen therapy. Clinical benefit or harm could not be excluded for the outcome of
 50 mortality or ECMO amongst those diagnosed with MAS [1.09 (0.86 to 1.39)], but 'routine
 51 tracheal suctioning' was possibly associated with lower risk of respiratory morbidities
 52 amongst those diagnosed with MAS. The CoE was very low for most of the outcomes
 53 evaluated.

54 **Conclusions:** Due to the very low CoE for the outcomes evaluated, no definitive conclusions
 55 can be drawn warranting the need for additional studies.

56 **Key words:** meconium, non-vigorous, tracheal suctioning, resuscitation, neonate

1. INTRODUCTION

In 2015, the Neonatal Task Force (NTF) of the International Liaison Committee on Resuscitation (ILCOR) suggested a change in the immediate approach to non-vigorous (NV) neonates born through meconium stained amniotic fluid (MSAF) from routine laryngoscopy and tracheal suctioning to immediate resuscitation without routine tracheal suctioning. Based on a systematic review of literature, the ILCOR NTF continued the suggestion of immediate resuscitation in NV MSAF neonates in its Consensus on Science with Treatment Recommendations (CoSTR) in 2020. (1,2) However, delivery room management of NV-MSAF neonates remains a topic of great debate (3) and the CoSTR emphasized that this was a weak recommendation based on very low certainty of evidence (CoE) from four small randomized controlled trials (RCTs), all originating from low-and middle-income countries (LMICs). The primary factor driving the treatment recommendation was avoiding harm associated with possibility of delaying ventilation while performing ‘routine tracheal suctioning’. (4–7) Following the implementation of this treatment suggestion, several observational studies with a before-and-after study design were published. Many of them were from high income countries (HICs) and aimed to evaluate the impact of this policy change on the various outcomes of NV-MSAF neonates.(8–20) Traditionally, meta-analyses are restricted exclusively to RCTs as the CoE derived from them are relatively higher when compared to that from observational studies.(21) Recent literature has indicated the usefulness of synthesizing data from observational studies, often termed as real-world evidence (RWE).(22) Henceforth, we performed this systematic review and meta-analysis of RWE from observational studies with a before-after design, evaluating the policy change from ‘routine tracheal suctioning’ to ‘no routine tracheal suctioning and immediate resuscitation’ in NV-MSAF neonates immediately after birth.

2. METHODOLOGY

The protocol was registered with PROSPERO (CRD42021269484) (23) and the systematic review is reported in accordance to Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines. (24) Since this was a secondary research of synthesis of data from published observational studies, an ethical committee approval was not applicable.

2.1. Literature Search

Medline, Embase, CENTRAL and Web of Science were searched from 1st January 2015 till 4th October 2022. Non-English studies were eligible for inclusion. Pediatric Societies conference abstracts were also searched for relevant studies. Conference abstracts were included if sufficient data was available. Hand searching of the references of the included studies was also performed. Two authors performed the literature screening independently using the portal Rayyan-QCRI (Doha, Qatar) . (25) Disagreements were resolved by consulting a third author. The search strategy is given in **Supplement Table 1**.

2.2. Inclusion criteria

Population: Neonates of any gestational age born through MSAF and who were NV at birth. NV was defined as when a neonate was not crying or breathing (or gasping) or was limp with poor tone or had bradycardia (heart rate of less than 100 beats per minute) at initial assessment immediately after birth. Since this was a pragmatic systematic review of RWE studies, and as MSAF is not recorded in some large databases such as the Vermont Oxford Network (VON), and definition of NV can be subjective, studies that had included a combination of NV-MSAF and vigorous MSAF neonates in the denominator were also included.

Intervention: Routine direct laryngoscopy and tracheal suctioning under laryngoscopy using a suction catheter or a meconium aspirator.

Comparator: No routine laryngoscopy and immediate initiation of positive pressure ventilation (PPV) if needed as per the ILCOR CoSTR after the initial steps of resuscitation. The

intervention and comparator as stated in the protocol registered in PROSPERO were switched post hoc for the purpose of ease of interpretability of results and because of the fact that this would not have any major bearing on the results of this meta-analysis.

Outcomes: The primary outcomes were mortality, a combined outcome of mortality or need for extracorporeal membranous oxygenation (ECMO) and proportion of neonates who were diagnosed with MAS (as defined by the study authors). The primary outcome of mortality or requirement of ECMO was included post hoc. Secondary outcomes included proportion of neonates requiring initial steps of resuscitation, non-invasive PPV through a self inflating bag or a T-piece resuscitator and invasive PPV (IPPV) through an endotracheal tube, chest compression or drugs, APGAR ≤ 3 at 1 minute and / or ≤ 7 at 5 minutes, requirement of NICU admission for any cause or for respiratory symptoms, requirement of non-invasive respiratory support (NRS), invasive mechanical ventilation (IMV), low flow oxygen therapy, duration of NRS, duration of IMV, duration of low flow oxygen support, surfactant treatment, receipt of inhaled nitric oxide (iNO) therapy, hypoxic ischemic encephalopathy (HIE) of any stage and \geq stage 2 (as defined by authors), ECMO and duration of hospital stay. All the outcomes were separately assessed for two groups of infants: Exclusively NV or a mixture of vigorous and NV-MSAF infants, and for those who were diagnosed with MAS subsequently.

Study design: Only observational studies with a before and after design were included. The “before” epoch included neonates who underwent ‘routine tracheal suctioning’ and the “after” epoch included neonates who were resuscitated with ‘immediate PPV without routine tracheal suctioning after the initial steps’ according to ILCOR CoSTR 2015 recommendation. One study (Kai-Li et al) reported immediate PPV in the before epoch and routine suctioning in the after epoch. (15)

Time frame: Since the new recommendation of ‘no routine ET suctioning’ was introduced after 2015, only studies published after this time were included.

2.2. Data extraction, data synthesis, risk of bias and CoE assessment

Two authors extracted the data independently using a pre-specified structured proforma. Meta-analysis was performed using the R software version 3.6.2 (Vienna, Austria). (26) The Mantel Haenszel method for binary outcomes and the inverse variance method for continuous outcomes were utilized. (27,28) Heterogeneity was assessed by Cochran Q, I^2 and τ^2 values.(29) A random effects model was preferred if I^2 value was $> 50\%$, and the large values were not attributed to differences between small and large magnitude of effect estimates.(30,31) Risk of Bias in Non-randomized Studies - of Intervention (ROBINS-I) was utilized for assessing the risk of bias in the included studies.(32) The CoE assessment for the effect estimates of various outcomes was performed using Grading of Recommendations, Assessment, Development and evaluations (GRADE) recommendations. (31,33–35) The results of the meta-analysis are communicated based on a modified GRADE group recommendation. (36) **(Supplement Table 2)**

2.3. Sub-group analyses

Sub-group analyses were performed for two categories of neonates based on the denominator specified in the included studies: exclusively non-vigorous MSAF neonates and a combination of vigorous and non-vigorous MSAF neonates. Sub-group analyses were also performed based on two levels of income classification: LMICs and HICs for the primary outcomes of mortality or ECMO amongst the MSAF neonates and those who developed MAS; and for the outcome of MAS.

3. RESULTS

Of the 1,424 records screened after the removal of duplicates, 359 full texts were retrieved for assessing the eligibility. Of these, 12 studies were included in the meta-analysis, (8–16,18-20)

and one in the narrative review. (17) The characteristics of the included studies is given in **Table 1**. The PRISMA flow is provided in **Figure 1**.

3.1. Risk of bias

Of the 12 studies included in the data synthesis, 10 studies had a serious risk (8,11–16,18-20) and one each had a moderate (9) and critical risk of overall bias. (10) (**Supplement Figure 2**) Most of the studies predominantly had a serious risk of bias for the domains of confounding and classification of interventions.

3.2. Primary outcomes

3.2.1. NV-MSAF / MSAF as denominator

3.2.1.1. Mortality or need for ECMO and Mortality: Meta-analysis of studies evaluating both NV and a combination of vigorous and NV-MSAF neonates as denominator indicated that clinical benefit or harm could not be excluded for the combined outcome of mortality or need for ECMO after the policy change from ‘routine tracheal suctioning’ to ‘no routine ET suctioning’ due to the effect estimate being statistically not significant {Relative risk [RR] [95% confidence interval (CI)]: 0.74 (0.47 to 1.17) and the CoE being very low. (**Figure 2, Supplement Table 3**). Clinical benefit or harm could not be excluded for the other primary outcome of mortality [RR 0.68 (0.42 to 1.11)], CoE being very low. (**Supplement Figure 1**). There was no statistically significant difference in the incidence of mortality/ECMO between studies done in LMIC and HIC.

3.2.1.2. Incidence of MAS:

Though clinical benefit or harm could not be ruled out from synthesis of studies that had evaluated a combination of vigorous and NV-MSAF for the outcome of MAS [RR 0.91 (0.36 to 2.27); CoE: Very low], the results from analysis of studies that had exclusively evaluated NV-MSAF neonates showed a possibly decreased risk of MAS in the ‘tracheal suction epoch’

when compared to the ‘no tracheal suction epoch’ [RR 0.60 (0.38 to 0.94)], CoE being very low. **(Figure 2, Supplement Table 3)**

3.2.2. MAS as denominator

3.2.2.1. Mortality or need for ECMO and Mortality: Sub-group analysis of studies that had exclusively included NV-MSAF neonates and who were later diagnosed with MAS showed that ‘tracheal suctioning’ possibly increased the risk of mortality or ECMO when compared to ‘no tracheal suctioning’ [RR 1.89 (1.08 to 3.29)], CoE being very low; clinical benefit or harm could not be ruled out for the sub-group including any MSAF as denominator RR 0.98 (0.75 to 1.29)], CoE being very low. **(Figure 2)** Clinical benefit or harm could not be excluded for primary outcome of mortality [RR 1.08 (0.70 to 1.66)], CoE being very low. **(Supplement Figure 1).** Sub-group analysis of studies exclusively evaluating NV-MSAF neonates showed ‘tracheal suctioning’ possibly had an increased risk of mortality when compared to ‘no tracheal suctioning epoch’ [RR 1.81 (1.02 to 3.23)], very low certainty. However, only 2 studies contributed to this analysis and was influenced by a single study from LMIC. **(Supplement Figure 1).**

3.3. Secondary outcomes

3.3.1. NV-MSAF/ MSAF as denominator

3.3.1.1. Delivery room outcomes: Sub-group evaluation of studies exclusively evaluating NV-MSAF neonates revealed that when compared to the post policy change epoch of ‘no tracheal suctioning’, ‘routine tracheal suctioning’ epoch had possibly lesser requirement of initial steps of resuscitation [RR 0.67 (0.49 to 0.92)], CoE being very low. **(Supplement Figure 3).** Clinical benefit or harm could not be ruled out for this sub-group for the other outcomes: APGAR <4 at 1 minute and ≤ 7 at 5 minutes, requirement of PPV, IPPV and requirement of advanced resuscitation (chest compression or drugs). **(Supplement Figure 3).**

3.3.1.2. Requirement of NICU admission for respiratory indications: Analysis of studies evaluating both NV and a combination of vigorous and NV-MSAF neonates as denominator indicated that when compared to ‘no tracheal suctioning’ group, ‘routine tracheal suctioning’ group had possibly lesser requirement of NICU admission for respiratory indications [RR 0.69 (0.53 to 0.90)], CoE being very low. The evidence was very uncertain for NICU admissions for other causes. **(Figure 3, Supplement Table 3)**

3.3.1.3. Respiratory outcomes: Evaluation of studies including both NV and a combination of vigorous and NV-MSAF neonates as denominator indicated that when compared to ‘no tracheal suctioning’ epoch, ‘routine tracheal suctioning’ epoch possibly had a lower risk of requirement of NRS [RR 0.55 (0.42 to 0.72)], IMV [RR 0.63 (0.45 to 0.88)], low flow oxygen therapy [RR 0.69 (0.56 to 0.86)], lesser duration of low flow oxygen {Mean difference (MD) 95% confidence interval (CI): -16 hours (-25.83 hours to - 6.17 hours)}, air leak [RR 0.40 (0.20 to 0.83)] and lesser surfactant therapy [RR 0.23 (0.09 to 0.59)], CoE being very low to low **(Figure 4 and Supplement Table 3)** Clinical benefit or harm could not be ruled out for the other respiratory outcomes: PPHN, iNO therapy, duration of NRS and duration of IMV and for the outcomes of HIE (any stage), HIE \geq stage 2, duration of hospital stay and requirement of ECMO **(Supplement Figure 4, Supplement Table 3).**

3.3.2. MAS as denominator

3.3.2.1. Delivery room outcomes: Meta-analysis of studies evaluating both NV and a combination of vigorous and NV-MSAF neonates who were later diagnosed with MAS suggested that when compared to ‘no tracheal suctioning’ epoch, the infants in the ‘routine tracheal suctioning’ epoch possibly had a higher risk of receipt of IPPV in the delivery room [RR 1.24 (1.05 to 1.47)], CoE being very low. Clinical benefit or harm could not be ruled out for the other delivery room outcomes. **(Supplement Figure 5, Supplement Table 4)**

3.3.2.2. Respiratory outcomes: Synthesis of evidence from studies that had included neonates who were either NV and a combination of vigorous and NV-MSAF as denominator revealed that ‘routine tracheal suctioning’ was possibly associated with lower frequency of surfactant treatment amongst those who were diagnosed with MAS when compared to the ‘no tracheal suctioning’ group [RR 0.88 (0.81 to 0.95)]. Further, ‘routine tracheal suctioning’ group who developed MAS possibly had a lower risk of NRS requirement [RR 0.69 (0.57 to 0.82)], lesser duration of NRS [MD -47 hours (-74.28 hours to -19.72 hours)] and IMV support [MD -51.65 hours (-95.37 hours to -7.92 hours)], CoE being very low for all the outcomes. **(Supplement Table 4)** Sub-group analysis of studies exclusively evaluating NV-MSAF neonates indicated that ‘routine tracheal suctioning’ group was associated with lesser risk of air leak [RR 0.33 (0.12 to 0.94)], CoE being very low. **(Supplement Figure 6, Supplement Table 4)** Clinical benefit or harm could not be ruled out for all the other outcomes evaluated. **(Supplement Figure 6, Supplement Table 4)**

3.4. Sub-group analyses based on income classification

There were no sub-group differences between the countries for the outcome of mortality or ECMO. **(Supplement Figure 7)** The incidence of MAS amongst NV-MSAF neonates was significantly lower in the ‘routine tracheal suctioning’ group when compared to the ‘no tracheal suctioning’ group when studies from HICs alone were analysed separately (RR; 95% CI: 0.45; 0.28 to 0.71). However, there was statistically significant sub-group difference between HICs and LMICs for the outcome of MAS (Sub-group difference p-value: 0.01). **(Supplement Figure 8)**

4. DISCUSSION

In this pragmatic systematic review and meta-analysis of RWE from observational studies with a before and after study design, we evaluated the impact of implementing the ILCOR CoSTR

2015 treatment suggestion of ‘no routine tracheal suctioning and immediate resuscitation’ on various outcomes of NV-MSAF neonates.(1) Three groups of neonates were evaluated: (i) NV-MSAF only or (ii) a pool of vigorous and NV-MSAF neonates, and (iii) infants diagnosed with MAS. Summarising our results, we found no conclusive evidence for changes in the composite primary outcome of mortality or need for ECMO in infants born through MSAF following the guidance change, but possibly an increased incidence of MAS, NICU admissions due to respiratory indications and other respiratory morbidities.

Only RWE was meta-analysed in this systematic review. No RCTs were published on this patient-intervention-control-outcomes (PICO) after the 2015 ILCOR CoSTR treatment suggestion. Recent literature has indicated the usefulness of synthesizing data from RWE which include wider generalizability and increased power with precision, especially when the existing literature is from small RCTs as is the case for this PICO of ‘routine tracheal suction’ versus ‘no routine tracheal suction’ in NV-MSAF neonates.(22, 37)

As evaluated in this meta-analysis, there was no difference in the primary outcome of mortality or need for ECMO between the two epochs when the denominator was NV-MSAF or a combination of vigorous and NV-MSAF, with the CoE being very low. In contrast, the NV-MSAF neonates in the ‘routine tracheal suctioning’ epoch possibly had a lower risk of MAS when compared to the ‘no tracheal suctioning’ epoch. Amongst the NV-MSAF neonates with MAS, the risk of combined outcome of mortality or need for ECMO and mortality was higher in the ‘routine suctioning’ epoch. These results were predominantly influenced by a study from a LMIC by Kumar et al. which contributed to maximum weightage in the meta-analysis.(14)

The high mortality with MAS in LMIC from HIE and PPHN, and lack of access to appropriate antenatal care, intrapartum fetal monitoring, and neonatal interventions such as therapeutic hypothermia, NRS, IMV, iNO and ECMO remains a significant challenge.(38–40)

276 The results from our meta-analysis indicate that other respiratory outcomes such as requirement
277 of NRS, IMV, low flow oxygen (requirement and duration), air leak and surfactant therapy
278 were significantly infrequent in the ‘routine tracheal suctioning’ epoch compared to ‘no
279 tracheal suctioning’ epoch. Even amongst the neonates who developed MAS subsequently,
280 ‘tracheal suction group’ had a lower frequency of surfactant therapy, reduced need as well as
281 duration of NRS and lesser IMV duration when compared to ‘no routine tracheal suction group’.

282 The results of this systematic review also indicated that NICU admissions for respiratory
283 indications were lower in the ‘tracheal suctioning’ group when compared to ‘no tracheal
284 suctioning’ group. It had been proposed that the pathophysiology of meconium aspiration is
285 predominantly initiated during the antepartum period and that mechanical airway obstruction
286 may have a limited role compared to other mechanisms, such as antenatal
287 inflammation/infection, surfactant inactivation and pulmonary hypertension.(41–44) The
288 findings of our systematic review emphasize the need for further research into the contribution
289 of immediate prepartum aspiration of meconium on respiratory pathophysiology. Several
290 factors have been reported to be associated with increased respiratory morbidity in neonates
291 born through MSAF, many of which could be anticipated before delivery. These include signs
292 of antenatal fetal distress, Caesarean section, thicker consistency of meconium and presence of
293 chorioamnionitis. (45–47) Whether a specific sub-group of NV-MSAF neonates with a
294 combination of some or all of these risk factors benefit from routine tracheal suctioning needs
295 to be researched further. Individual patient data meta-analysis from the published RCTs could
296 also aid in delineating the sub-group of NV-MSAF neonates who are appropriate candidates
297 for routine tracheal suctioning.

298 The results of our systematic review differ from the recent ILCOR systematic review by
299 Trevisanuto et al. and many other systematic reviews published on this PICO.(48–51) In the
300 meta-analysis by Trevisanuto et al., four RCTs (4-7) and one observational study (9) were

included and all of them had small sample sizes. While 3,018 neonates from observational studies were evaluated by our systematic review for the outcome of MAS, Trevisanuto et al.'s meta-analysis had a sample size of 581 neonates from the RCTs and 231 neonates from a single observational study. The other major reason for differences in results between our review and that of others could be due to the important fact that we had included only observational studies with a before-and-after study design. Such meta-analysis of RWE is known to have several limitations. These include selection bias, confounding and heterogeneity. Adjusted analysis using multivariate logistic regression is advocated for addressing many of these deficiencies.(52) However, only the study by Chiruvolu et al. had adjusted for baseline sickness.

(9)

Evaluation of secondary outcomes from studies which included NV-MSAF or a combination of vigorous and NV-MSAF neonates revealed that lesser proportion of neonates in the 'tracheal suctioning' group required initial steps of resuscitation, though these were not reflected in the outcomes of APGAR score at 1 minute and 5 minutes. Possible stimulation of the newborn during laryngoscopy might be a plausible reason for this finding. Amongst those who developed MAS, the 'tracheal suctioning' epoch also had higher rates of IPPV in the delivery room, which could be explained by the hypothesis that physicians might have preferred continuing ongoing PPV with an ET tube in-situ previously inserted for ET suctioning.

There were several limitations to this review. Firstly, it was a pragmatic review including only RWE from observational studies. Hence, significant confounding could be expected as most of the studies had not used appropriate statistical methods for matching baseline sickness profile of the two groups. Secondly, there was contamination with vigorous MSAF neonates in some of the included studies. Although these were balanced between the two groups this was addressed by sub-group analyses for all the outcomes where these studies were evaluated separately. The definition of MAS was widely variable between the included studies and could

have had a major bearing on the outcome as evaluated in this systematic review. This was a combination of observational studies from LMIC and HIC with varying access to therapy. In addition, there have been rapid improvements in NRS (53) and increased awareness of benefit of surfactant in MAS which could have influenced some results. (54) One of the articles was written in Chinese and had the reverse order (no-routine suction first followed by routine-suction epochs). (15) We could not reach these authors for clarification. Finally, most of the included studies had a serious risk of overall bias and the CoE was very low making many of the results of our meta-analysis uncertain.

5. CONCLUSION

Clinical benefit or harm from ‘routine tracheal suctioning’ could not be ruled out for the combined outcome of mortality or requirement of ECMO for NV-MSAF or a combination of vigorous and NV-MSAF neonates. Routine tracheal suctioning in NV-MSAF might possibly be associated with decreased risk of MAS and other respiratory outcomes such as NRS requirement, need for IMV, low flow oxygen, air leak and surfactant requirement. Due to very low to low CoE for most of the outcomes, the results of our review are uncertain. Observational studies with a before and after design evaluating the impact of the policy change to ‘no routine tracheal suctioning and immediate PPV when needed’ should enrol a homogenous population of NV-MSAF and report on outcomes adjusting for baseline sickness. Our findings call for large RCTs evaluating ‘routine tracheal suctioning’ versus ‘no routine tracheal suctioning and immediate PPV when needed’ in NV-MSAF neonates separately in HIC and LMIC. (55) However, lack of equipoise, difficulty in obtaining consent and lack of evidence of increasing incidence of MAS following implementation of no-routine tracheal suction guidelines are factors that suggest that novel alternate designs such as multicenter, observational registries or a cluster-randomization approach may need to be considered.

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FIGURE LEGENDS

Figure 1: PRISMA flow

Figure 2: Forest plot depicting the effect estimates for the primary outcomes: mortality or requirement of ECMO and MAS

Figure 3: Forest plot depicting the effect estimates for the outcomes: requirement of NICU admission for respiratory symptoms and NICU admission for any reasons.

Figure 4: Forest plot depicting the effect estimates for the outcomes: requirement of non-invasive respiratory support (NRS), invasive mechanical ventilation (IMV), low flow oxygen requirement, air leak and receipt of surfactant with meconium stained amniotic fluid (MSAF) as denominator

TABLE LEGENDS

Table 1 - Characteristics of the included studies

