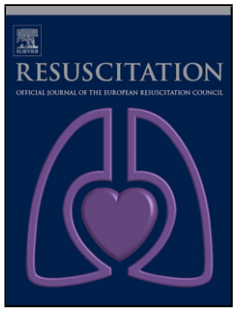

Title: Supraglottic Airway Devices during Neonatal Resuscitation: An historical perspective, systematic review and meta-analysis of available clinical trials

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Supraglottic Airway Devices during Neonatal Resuscitation: An historical perspective, systematic review and meta-analysis of available clinical trials

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Abbreviations:

LM	- Laryngeal mask
NICU	- Neonatal intensive care unit
RCT	- Randomized control trial
CPAP	- Continuous positive airway pressure
OR	- Odds ratio
CI	- Confidence intervals
NNT	- Number needed to treat
RR	- Relative Risk

Abstract

Introduction

Various supraglottic airway devices are routinely used to maintain airway patency in children and adults. However, oropharyngeal airways or laryngeal masks (LM) are not routinely used during neonatal resuscitation.

Method

The aim of this article was to review the available literature about the use of supraglottic airway devices during neonatal resuscitation. We reviewed books, resuscitation manuals and articles from 1830 to the present using the search terms “Infant”, “Newborn”, “Delivery Room”, “Resuscitation”, “Airway management”, “Positive Pressure Respiration”, “Oropharyngeal Airway” and “Laryngeal Mask”.

Results

No study was identified using oropharyngeal airways during neonatal resuscitation. Four trials including 509 infants compared positive pressure ventilation with a LM, bag and mask or an endotracheal tube. Infants in the LM group were intubated less frequently compared to infants in the bag and mask ventilation group 4/275 vs. 28/234 (OR 0.13, 95% CI 0.05-0.34). Infants resuscitated with the LM had significantly less unsuccessful resuscitations 4/275 vs. 31/234 (OR 0.10, 95% CI 0.03-0.28). Two trials including 34 preterm infants compared surfactant administration via LM vs. endotracheal tube. LM surfactant administration was safe and no adverse events were reported.

Conclusion

The efficacy and safety of oropharyngeal airways during neonatal resuscitation remain unclear and randomized trials are required. The current evidence suggests that resuscitation with a LM is a feasible and safe alternative to mask ventilation in infants >34 weeks gestation and birth weight >2000g. However, further randomized control trials are needed to evaluate short- and long-term outcomes following use of laryngeal masks. In addition, surfactant administration via LM should be used only within clinical trials.

Introduction

Approximately 10% of newborn infants require some form of respiratory support in first minutes after birth[1]. The International Liaison Committee On Resuscitation (ILCOR) and various national guidelines recommend techniques and equipment for neonatal resuscitation[2-5]. They all agree that mask ventilation is the cornerstone of respiratory support immediately after birth[2-5]. However, several factors can reduce the effectiveness of mask ventilation, including poor face mask technique resulting in leak or airway obstruction, spontaneous movements of the baby, movements by or distraction of the resuscitator, and procedures such as changing the wraps or fitting a hat[6-8]. Delivery room studies have shown that mask ventilation is difficult and mask leak and airway obstruction are common[6,7,9,10]. Various airway maneuvers (e.g. neutral position, chin lift or jaw thrust) have been recommended to optimize mask ventilation and reduce airway obstruction[8]. Resuscitation guidelines suggest that 'in floppy babies application of jaw thrust or the use of an appropriately sized oropharyngeal airway, which may be helpful in opening the airway'[4]. Although oropharyngeal airways are frequently used for airway patency in children and adults[11-13], none are routinely used during neonatal resuscitation.

Archie Brain, a British anesthetist, described the laryngeal mask (LM) as an alternative to endotracheal intubation in 1981[14]. The LM consists of an airway tube connected distally to a soft elliptical mask with an inflatable rim to fit over the laryngeal inlet whereas the proximal end connects to the positive pressure ventilation device[14]. A LM provides an alternative in difficult airway scenario where either mask ventilation is ineffective or intubation impossible[15]. Currently LMs are routinely used by paramedics, emergency rooms and operating theaters for adult and pediatric anesthesia[12,16,17]. In newborn infants, the evidence is mainly derived from case series and observational studies[18,19], suggesting that a LM can provide an effective rescue airway during resuscitation if both mask ventilation and endotracheal intubation have been unsuccessful. Current neonatal resuscitation guidelines recommend use of LM in newborn infants > 34 weeks gestation or > 2000 gram birth weight when face mask ventilation or tracheal intubation is unsuccessful or not feasible[2,4]. In addition, use of LMs have been reported during neonatal transport[20-22], provision of prolonged mechanical ventilation in particular for infants with upper airway abnormalities [23-27], and administration of intratracheal medications[28-32]. Although, LMs are recommended

by various neonatal resuscitation guidelines[2-4], if mask ventilation or endotracheal intubation have been unsuccessful, they are not routinely used during neonatal resuscitation.

The aim of this article was to review the available literature on the use of oropharyngeal airways and laryngeal mask airway during neonatal resuscitation.

Methods

Search strategy for historical perspective and systematic review of available literature

We reviewed books, resuscitation manuals and articles from 1830 to the present with the search terms "Infant", "Newborn", "Delivery Room", "Resuscitation", "Airway management", "Positive Pressure Respiration", "Oropharyngeal Airway" and "Laryngeal Mask". We used the standard methods of the Cochrane Neonatal Review Group for inclusion, review, and quantitative methods.

Data sources and search strategy for meta-analysis

We searched Medline (1980 - May 2012) and Embase (1980 - May 2012) using the following MeSH database search terms: "Infant", "Newborn", "Airway Management", "Resuscitation", "Positive Pressure Respiration" and "Oropharyngeal airways" "Laryngeal Mask". The search was limited to human RCTs with no language restrictions (Table 2). We also searched clinicaltrials.gov for completed (Table 3) and ongoing trials (Table 4) using similar search terms, reviewed abstracts from the Pediatric Academic Society annual meetings (2000–2010), and performed a manual search of references in narrative and systematic reviews on laryngeal masks. The full search strategies for PubMed and EMBASE are detailed in Appendix 1.

Study selection

Two authors (GMS, COFK) independently screened titles and abstracts for potential eligibility and full texts to confirm eligibility (Table 2). When discrepancies arose, a third party was consulted. Data were extracted using a standardized data collection form to record study design and methodological characteristics, patient characteristics, interventions, outcomes, and missing outcome data (Table 3).

Data synthesis and analysis

The analyses were performed using Review Manager 5.0. Dichotomous data were expressed as odds ratio (OR) with 95% confidence intervals (CI). For all analyses, we used a fixed-effect model. The number needed to treat (NNT) was derived from the Relative Risk (RR) in meta-analyses where the 95% CI (or the RR) did not include zero. Heterogeneity was explored using a chi-square test, and the quantity of heterogeneity was measured using the I^2 statistic.

Results

No published RCT investigating oropharyngeal airways was identified. However, one trial is currently evaluating the use of an oropharyngeal airway in preterm infants receiving mask ventilation [33] (Table 4). Four RCTs comparing LM vs. mask ventilation or endotracheal intubation were found. Several RCTs investigating surfactant administration via LM have been identified[34-37] (Table 4).

Oropharyngeal airways

Sir Fredrick Hewitt recognized that upper airway obstruction was a common problem during general anesthesia[38]. In 1907 he presented the first known artificial oral 'air-way' (Table 1)[38-40]. Following Hewitt, Lumbard[41] and Waters[42] also developed oropharyngeal airways (Table 1). In 1933 Arthur Guedel presented a black rubber modification of the metal Water's airway "the Guedel Oropharyngeal airway" (Figure 1)[43]. The Guedel airway was designed to hold the tongue away from the back of the pharynx, thus providing a clear channel for respired gases[44]. Oropharyngeal airways may be used to open the airway in floppy newborn infants, or if mask ventilation is ineffective[4,45-48]. In addition, various surveys evaluating neonatal resuscitation practice reported that Guedel airways are part of the neonatal resuscitation equipment[5,49]. Guedel airways for preterm and term infants come in traditional sizes of 000, 00, and 0 (Figure 1). However, several studies compared the design of available Guedel airways and reported obvious shape and length differences, despite being labeled the same size[50-52]. The use of oropharyngeal airways during neonatal resuscitation has not been systematically studied. No study addressing the use of an oropharyngeal airway during neonatal resuscitation was identified. Currently, one RCT is

comparing an oropharyngeal airway for prevention of airway obstruction during positive pressure ventilation in preterm infants < 34 weeks gestation during neonatal resuscitation[33].

Laryngeal Mask airway

Available Laryngeal Airway Masks

In 2004, Trevisanuto et al. reported that although 35% of Italian anesthesiologists and 23% of pediatricians have experience with LMs[53] for airway management in newborn infants. Anesthesiologists were more enthusiastic about the LM than pediatricians. The education level, competence and utilization rates of LM during neonatal resuscitation was similar in both groups[53]. Gandini et al. assessed the knowledge about LMs in 80 health care providers in Australia and reported similar results[54]. Thirty-one percent had not heard of the LM, 57% did not know the LM could be used for neonatal resuscitation and 88% thought it was a disposable device[54]. Laryngeal mask size and infants birth weight are the main limitation for LM use in newborn infants. A size 1 LM is recommended for all infants < 5 kg. Observational and randomized studies have demonstrated that a size 1 LM can be used in term and preterm infants >34 weeks or > 2000g. However, currently data for the use of LMs for preterm infants are lacking although, successful resuscitation of premature infants with birth weights as low as 800 g have been reported[55,56].

Currently, there are various LMs available e.g. i) LMA Classic™, LMA ProSeal™ and LMA Supreme™ (LMA North America Inc., San Diego, CA, USA), ii) i-gel™ supraglottic airway (Intersurgical, Liverpool, NY, USA) or iii) Air-Q™ Disposable Laryngeal Mask Airway (Mercury Medical, Clearwater, FL, USA).

The LMA Supreme™, i-gel™ and Air-Q™ are disposable single use LMs compared to reusable and therefore more expensive LMA Classic™, LMA ProSeal™. The i-gel™ supraglottic airway has a non-inflating soft-gel cuff compared to inflatable cuffs with all other LMs. A non-inflating soft-gel cuff potentially might reduce reported soft tissue trauma[57-59]. There is the potential for gastric distension, although this has never been reported in newborn infants[12,25,60-62]. The LMA ProSeal™ and LMA Supreme™ have a gastric vent for air removal from the stomach in cases where gastric distension compromised positive pressure ventilation. Although, various studies compare laryngeal masks from LMA North America Inc., randomized control trials comparing the performance of each LM are warranted.

Mannequin studies

The skills needed to successfully insert any LM (Figure 3) can be acquired using neonatal mannequins[54,55,63,64]. After a 15 minute educational session using a mannequin Gandini et al. found that the mean time to successfully insert a LM was five seconds [54]. Micaglio et al.[63] compared time from insertion to the first inflation of an artificial lung for the LMA Classic™ and the LMA ProSeal™. The success rates of the first attempt were significantly higher with the LMA Proseal™ compared to the LMA Classic™ (97% vs. 92%)[63]. However, there was no difference in the mean insertion time, 10 seconds for the LMA Classic™ and 11 seconds for the LMA Proseal™. Trevisanuto et al. compared LMA Supreme™, Classic™, and Proseal™ in a mannequin study to assess time to establish adequate ventilation, and ease of insertion[55]. The success rate to insert a LM with the first attempt was comparable among the three devices. The mean time to establish effective ventilation was significantly lower with the Supreme LMA™ (12 seconds) compared to the LMA ProSeal™ (19 seconds), however it was similar compared to the LMA Classic™ (15 seconds)[55]. Micaglio et al. compared delivered peak inflation pressures between the classic and LMA Proseal™[64]. Both LMs delivered similar pressures with a set peak inflation pressure of 10-20 cm H_2O[64]. However, the LMA Classic™ was unable to deliver peak pressures higher than 24 cm H_2O even though the set pressures were 30, 35 or 40cm H_2O[64]. The LMA Proseal™ was able to deliver all of the set pressures[64]. This study suggested that the LMA Proseal™ provides a better laryngeal seal during positive pressure ventilation. However, the study was performed in a mannequin, which has distinctive differences compared to newborn infants[65]. Proficiency in endotracheal intubation cannot be achieved with mannequin practice alone[66-69]. However, mannequin studies suggest that proficiency in LM insertion techniques can be achieved with a 15-minute educational session[54,55,63,64]. Clinical trials are urgently needed as this device has the potential to change resuscitation practices around the world and may lead to LMs becoming the primary resuscitation device in near term and term infants.

Laryngeal mask during neonatal resuscitation

Observational studies

Laryngeal masks have been recommended as rescue airway if mask ventilation or endotracheal intubation is unsuccessful or not feasible[4]. The available evidence in newborn

infants comes from case series, cohort studies and four RCTs (Table 2). Paterson et al. reported the first prospective study evaluating LM for newborn infants ≥ 2.5 kg and gestation ≥35 weeks[70]. They demonstrated that the LM could be successfully inserted with first attempt on all 21 newborn infants[70] and 20 of these infants were successfully resuscitated without any complications[70]. Trevisanuto et al. compared 95 newborn infants > 34 weeks gestation receiving respiratory support via LM with a historical control group[71]. 94/95 newborn infants were successfully resuscitated using LM. The need for tracheal intubation was almost halved using LM (67% to 34%)[71]. Gandini et al. retrospectively analyzed LM use in 104 newborn infants requiring positive pressure ventilation during neonatal resuscitation[72]. They reported that the LM was successfully inserted in first attempt in all 104 newborn infants and 103/104 newborn infants were successfully resuscitated[72]. Zanardo et al. reported that resuscitation of late preterm infants (34-37 weeks gestation) using a LM was associated with lower NICU admissions rates and shorter length of stay compared to mask-ventilation or endotracheal intubation[73]. In addition, newborn infants resuscitated with LM had higher Apgar scores, required less respiratory support and NICU admission compared to newborn infants receiving endotracheal intubation[62].

Meta-analysis of randomized trials

We identified four RCTs (Table 2) which included a total of 534 infants comparing LM with endotracheal tube or facemask ventilation[58,61,74,75]. Two RCTS compared LM versus mask ventilation. Singh et al. randomized 50 infants > 35 weeks gestation to either LM or mask ventilation in the delivery room[74]. Both devices had similar success rates, rates of endotracheal intubation, and Apgar scores[74]. Zhu et al. randomized 369 newborn infants (>34 weeks or >2000 grams) to receive respiratory support either with LM or bag and mask immediately after birth[61]. Laryngeal masks were successfully inserted with the first attempt in 98.5% with a mean (SD) insertion time of 7.8 (2.2) seconds. LM group had significant higher successful resuscitation rates, less endotracheal intubations, and shorter total ventilation times. Esmail et al. compared LM versus endotracheal intubation during neonatal resuscitation in 40 newborn infants[58]. No significant differences between insertion time, failure rate with 1st attempt, resuscitation outcomes or traumatic airway events were reported[58]. Feroze et al. compared LM versus endotracheal tube or facemask ventilation in

75 infants >1500g birth weight[75] and reported no difference in insertion time. However, the time for effective resuscitation was doubled in the bag and mask group compared to the LM group[75]. Three RCTS reported the number of intubations when either LM or bag and mask ventilation failed to provide adequate ventilation. Fewer infants in the LM group required intubation compared to the mask ventilation group 4/275 vs. 28/234 (OR 0.13, 95% CI 0.05-0.34, NNT 10 to prevent one intubation) (Figure 2). Two RCTs (Figure 2) contributed a small number of infants and the majority of data come from the RCT by Zhu et al. Therefore, these results should be interpreted with caution. The operators in three trials were anesthetists which are more likely familiar with LM insertion[58,74,75]. Feroze et al. reported a very short intubation time of only 9 seconds[75]. The study by Zhu et al. was quasi-randomized and their publication did not provide a CONSORT-chart, a consent process or blinding[61]. All infants in Zhu et al. study were resuscitated with 100% oxygen[61]. In addition, 26 infants in the mask group were intubated after only 66 sec of mask ventilation, which potentially was rushed[61]. Overall, RCTs have shown that initial respiratory support with a LM is feasible and safe. However, there is not enough evidence to recommend LM instead of mask ventilation for initial respiratory support in the delivery room and large randomized trials are warranted before the technique is widely applied.

Surfactant administration

Available evidence comes from 17 newborn infants described in case reports and 34 infants included in RCTs[28,30,76-78]. Brimacombe et al. described surfactant administration via LM in one term and one preterm infant of 30 weeks gestation[30,76]. Both infants showed improvement after surfactant administration. Brimacombe et al. suctioned the nasogastric tube which yielded 1.7 ml of surfactant suggesting that 3.3 ml had entered the lungs[28,30]. Trevisanuto et al. reported the feasibility and practicality of administering surfactant via LMA in 12 preterm infants with a median gestational age of 31 weeks[19,76]. In eight preterm infants, a significant increase in the mean arterial to alveolar oxygen tension ratio was observed. However, in four no improvement was observed, suggesting a large portion of surfactant did not reach the lungs of these infants. Micaglio et al. used a nasogastric tube to administer surfactant in three preterm infants[28,31,32]. Two RCTs reported surfactant administration via a LM[77,78]. Stewart et al. compared surfactant administration via LM (n=8) vs. continuous positive airway pressure (CPAP) + oxygen and no surfactant (n=5) in preterm

316 infants >1200g birth weight within 72 hours of age[77]. Infants who received surfactant via a
317 LM had lower oxygen requirements. However, the trial was terminated due to low
318 enrolment (Table 3)[34]. Santana-Rivas et al. compared surfactant administration via
319 endotracheal intubation (n=10) vs. LM (n=9) in preterm infants between 29 and 37 weeks[78].
320 After surfactant administration infants were returned to nasal CPAP if possible[78]. Failure of
321 nasal CPAP after surfactant administration was 90% in the intubation groups compared to
322 22% in the LM group (p=0.003)[78]. Neither RCT reported any adverse events during
323 surfactant administration via a LM. In comparison, surfactant administration via an
324 endotracheal tube has been associated with a series of adverse events[32,79-83]. Although, pilot
325 data are promising, the current available evidence suggests that surfactant administration
326 via laryngeal mask should be limited to clinical trials (Table 3).
327
328 *Epinephrine administration*
329 There is little evidence evaluating the safety and efficacy of administering epinephrine to
330 newborn infants through a LM. Epinephrine administration, via LM, has been studied in
331 animal models and during adult cardio-pulmonary resuscitation[31,32]. Chen et al. compared
332 administration of epinephrine via intravenous, endotracheal, injection in the upper end of
333 the LM and via a catheter through the LM, in a non-arrest adult porcine model[32]. No
334 difference in peak plasma epinephrine levels, mean arterial blood pressure and heart rate
335 were found between endotracheal and injection via a catheter through the LM[31,32].
336 Although the lowest peak plasma epinephrine level was reported when epinephrine was
337 injected in the upper end of the LM[32], mean arterial blood pressure and heart rate were
338 similar to endotracheal epinephrine administration[32,56]. Liao et al. randomized 30 piglets to
339 receive different epinephrine doses through either endotracheal tube or LM via a
340 catheter[31]. Piglets in the endotracheal tube group received 50-microgram/kg epinephrine
341 and piglets in the LM groups were divided to receive either two, four or six-fold dose of
342 epinephrine compared to the endotracheal tube dose[31]. After epinephrine administration,
343 piglets in the endotracheal tube group and the six fold LM group had elevated arterial
344 pressures one min after administration[31]. Piglets in the two and four fold group did not
345 show any increase in hemodynamic parameters[31]. This may suggest need for higher dose via
346 LM. One case report described an immediate response of an 800g newborn infant to the

administration of epinephrine through a laryngeal mask [56]. The current available evidence does not allow any recommendations for epinephrine administration.

Neonatal transport

Five cases of LM use during neonatal transport have been reported[20-22,27,84]. Fraser et al. reported inter-hospital transfer of two infants with type 3 laryngotracheo-oesophageal clefts[22]. Trevisanuto et al. described two infants with congenital airway malformations during inter-hospital transport[20,26]. Brimacombe et al. described a newborn infant with sudden apneic episodes during helicopter transport[21]. The median (IQR) gestational age and birth weight of these five infants was 36 (35-40) weeks and 2800 (2610-2900) grams, respectively. All five infants required rescue airway management with LM as both bag and mask ventilation or endotracheal intubation either failed or were not feasible[20-22,27,84]. All infants were successfully managed with a size 1 LM and none received any sedatives or anesthetic drugs prior to LM insertion[20-22,27,84]. These five cases demonstrate the potential use of LM during neonatal transport. In particular during air transport endotracheal intubation is almost impossible due to vibrations, limited space and access to the infants head; hence neonatal air transport services might consider LM as part of their equipment. However, RCTs are needed to compare endotracheal intubation versus LM during neonatal transports.

Long-term mechanical ventilation

Laryngeal masks have been primarily used for short-term airway support in newborns. Their safety during long-term ventilatory support has not been established. Several case reports have described LM to provide mechanical ventilation up to 6 days without apparent complications[23-25,27,61,85-88]. In addition, Fraser et al. reported one case of Type 3 laryngo-tracheo-esophageal cleft in a 35 weeks preterm infant who received high frequency oscillation over 10 hours via a laryngeal mask airway suffering from acute respiratory failure[26,61]. Although, these case reports demonstrate that a LM can be used for long-term ventilation, a small animal model of prolonged LM use raises significant concerns[84]. Ferrets ventilated with a laryngeal mask developed significant lingual edema and cyanosis after 6 to 16 hours resulting in airway obstruction[84]. Histologic examination showed venous and capillary congestion. The investigators found that it was difficult to suction the airway

effectively through the LM, and tenacious secretions contributed to respiratory compromise[84]. Although, case reports have demonstrated that LMs can be used for prolonged ventilation, randomized studies are required to determine long-term effects of laryngeal mask placement.

"Can't ventilate, can't intubate" situation

Although several delivery room studies reported complication with mask ventilation and endotracheal intubation[7,9,10,67-69,89], the incidence of "can't intubate, can't ventilate" situation has not been reported in newborn infants. In comparison it has been estimated 0.01-2 per 10,000 adult cases[90]. However, the majority of newborn infants can adequately ventilated and oxygenated using a mask when found unexpectedly difficult to intubate[7]. Brimacombe et al. reported a "can't intubate, can't ventilate scenario" in an 800g preterm infant in a rural hospital where mask ventilation and intubation was impossible[56]. Intubation failed to achieve increase in heart rate and adequate ventilation was only possible with a size 1 LM without inflating the cuff[56]. Fortunately, this is a very rare scenario in the daily neonatal practice. However, neonatologists should be aware of the potential of a "can't intubate, can't ventilate" situation and be familiar with alternative techniques to achieve a patent airway (e.g. laryngeal mask placement, airway manoeuvres[8], bronchoscopic intubation[91], or video-laryngoscope[92]) .

Safety of Laryngeal mask airways

A survey of almost 12 000 patients ranging from infant to adults reported critical incidents related to LM management in only 18 (0.15%) cases[70,93,94]. Complications have also been described during and after the use of LM in infants and older children[70,95-97]. Bronchoscopic studies have noted that the mask is often improperly seated and partially obstructs the laryngeal opening[27,28,30,70,76]. Few complications have been reported in newborn infants include vomiting[58,61], regurgitation[58,61], soft tissue trauma[57-59], laryngospasm, breath holding[12,21,25,61,62], vomiting, stridor, and desaturation after LM removal. However, no episodes of airway trauma, obstruction, or laryngospasm were reported in the neonatal case series and retrospective cohorts of Paterson, Gandini, Trevisanuto, and Zanardo[62,70-72,94]. LM can be correctly positioned with the 1st attempt[70,94,94] and insertion techniques are quickly learnt by unskilled operators[70,94,96,97]. Case series reported that LM insertion is less

invasive and faster compared to endotracheal intubation[28,30,70,76,98]. Esmail et al. found a higher 1st attempt failure rate in the LM group compared with those managed with an endotracheal tube[99]. However, the operators in this RCT were anaesthesiologists who had a much higher intubation success rate. These findings contrasted with those of Zhu et al. who found better 1st attempt success with LM when used by paediatricians[61]. Disadvantages of LMs include: i) time to start ventilation compared to bag and mask ventilation[57,59,60], ii) potential of gastric distension and gastric aspiration, although never reported in newborn infants[12,25,60-62], iii) laryngospasm[38,94], iv) development of complete or partial airway obstruction[41,94], v) perfect positioning of LM was observed in only 44% of all cases[40,94], vi) soft tissue injury in the uvula, oropharynx, epiglottis[98,100], impossibility to suction airway[42,84,101].

Gaps in the knowledge

No study has investigated the additional use of a Guedel airway during mask ventilation to reduce airway obstruction or mask leak. It is possible that lifting the tongue as expected action of a Guedel airway might reduce airway obstruction during mask ventilation.

Although there is increasing evidence that a LM has a role in neonatal airway management, further RCTs are needed. Of particular interest are long-term outcomes as cohort studies reported shorter duration of ventilatory support for infants admitted to the NICU. Randomized studies comparing i) available LMs versus bag and mask or endotracheal ventilation, ii) surfactant and epinephrine administration via LM versus endotracheal tube or nasogastric tube, iii) chest compression, during LM vs. bag and mask or endotracheal tube ventilation is required. In addition, studies addressing the potential use of LM in very small preterm infants and their effect on long-term outcomes are warranted. Furthermore, studies addressing the most efficient insertion technique to teach all medical professionals involved in neonatal resuscitation are necessary.

Conclusion

Efficacy and safety of oropharyngeal airways during neonatal resuscitation remain unclear and randomized trials are needed. The current evidence suggests that resuscitation with a LM is a feasible and safe alternative to mask ventilation in infants >34 weeks gestation and

442 birth weight >2000g. However further randomized control trials are needed to demonstrate
443 clinical short- and long-term benefits of laryngeal masks.

444

Appendix #1: Search strategies for meta-analysis (online supplement)

Search strategy for PubMed: last performed on 02/07/2012

Limits activated: "Publication date from 1980/01/01 to 2012/05/12", "Humans", "Clinical Trial", "Infant: birth-23 months"

#1 MeSH descriptor Infant explode all trees (Result: 36,866)
#2 MeSH descriptor Newborn explode all trees (Result: 17,541)
#3 MeSH descriptor Airway management explode all trees (Result: 1,504)
#4 MeSH descriptor Resuscitation explode all trees (Result: 1,074)
#5 MeSH descriptor Positive Pressure Respiration explode all trees (Result: 378)
#6 MeSH descriptor Laryngeal Mask explode all trees (Result: 116)
#7 ((#1) AND #2) AND #3 (Result: 1,103)
#8 (#7) AND #4 (Results: 689)
#9 (#7) AND #5 (Results: 304)
#10 (#7) AND #6 (Results: 20)
#11 (#7) AND #4) AND #6 (Results: 7)

Search Strategy for Embase: last performed on 02/07/2012

Limits activated: "Human", "1980 -Current", and "infant <to one year>"

#1 Infant (Result: 91,122)
#2 Newborn (Result: 91,122)
#3 Airway management (Result: 133)
#4 Resuscitation (Result: 739)
#5 Positive Pressure Respiration (Result: 353)
#6 Laryngeal Mask (Result: 139)
#7 ((#1) AND #2) AND #3 (Result: 133)
#8 (#7) AND #4 (Results: 17)
#9 (#7) AND #5 (Results: 7)
#10 (#7) AND #6 (Results: 32)
#11 (#7) AND #4) AND #6 (Results: 7)

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Table 1: Timeline of oropharyngeal airway devices (online supplement)

1834	J. Blundell describes digital intubation for the treatment of Asphyxia Neonatorum[101]
1895	A. Kirstein invented the modern Laryngoscope[99]
1908	F.W. Hewitt describes a straight rubber tube, known to be the first artificial oral 'air-way'[43]
1915	J.E. Lumbard describes his controller of the tongue and palate during general anesthesia[46]
1922	F.W. Hewitt modified his airway into a curved rubber tube[43] (Figure 1)
1928	P.J. Flagg described his technique of introducing a metal tube into the trachea using a small electrically lighted laryngoscope[100]
1930	R.M. Waters metal oropharyngeal airway, which had a straight bite-block section, an anatomically curved pharyngeal section, and an oval flange at the proximal end to prevent over insertion[47]
1933	A.E. Guedel describes the first oropharyngeal airway made of rubber with a small metal inlet as bite block[48] (Figure 1)
1935	J.B. Blaikley and G.F. Gibberd suggest to use a rubber catheter instead of the rigid tube for endotracheal intubation[102]
1950	R.A. Berman designed the first reusable oropharyngeal airway made of plastic[103]
1981	A. Brain designed the Laryngeal mask airway[14]
1988	Laryngeal mask airway becomes commercial available[104]
1990	N.M. Denny described the 1st neonatal resuscitation using a LMA[105]
1999	Only case reported were laryngeal mask was used for epinephrine administration during cardio-pulmonary resuscitation[59]
2004	1st surfactant administration via laryngeal mask airway in newborn infant[30]
2002, 2005, 2008, 2011	RCTs comparing LMA versus mask ventilation or endotracheal intubation[72-75] (Table 3)
2008, 2011	RCTs comparing LMA versus endotracheal tube for surfactant administration[78,79]
2012-ongoing	Oropharyngeal airway to reduce severe airway reduction[33] (Table 4)
2012-ongoing	3 RCTs comparing LMA versus endotracheal tube for surfactant administration[35-37] (Table 4)

Table 2: PRISMA flow chart

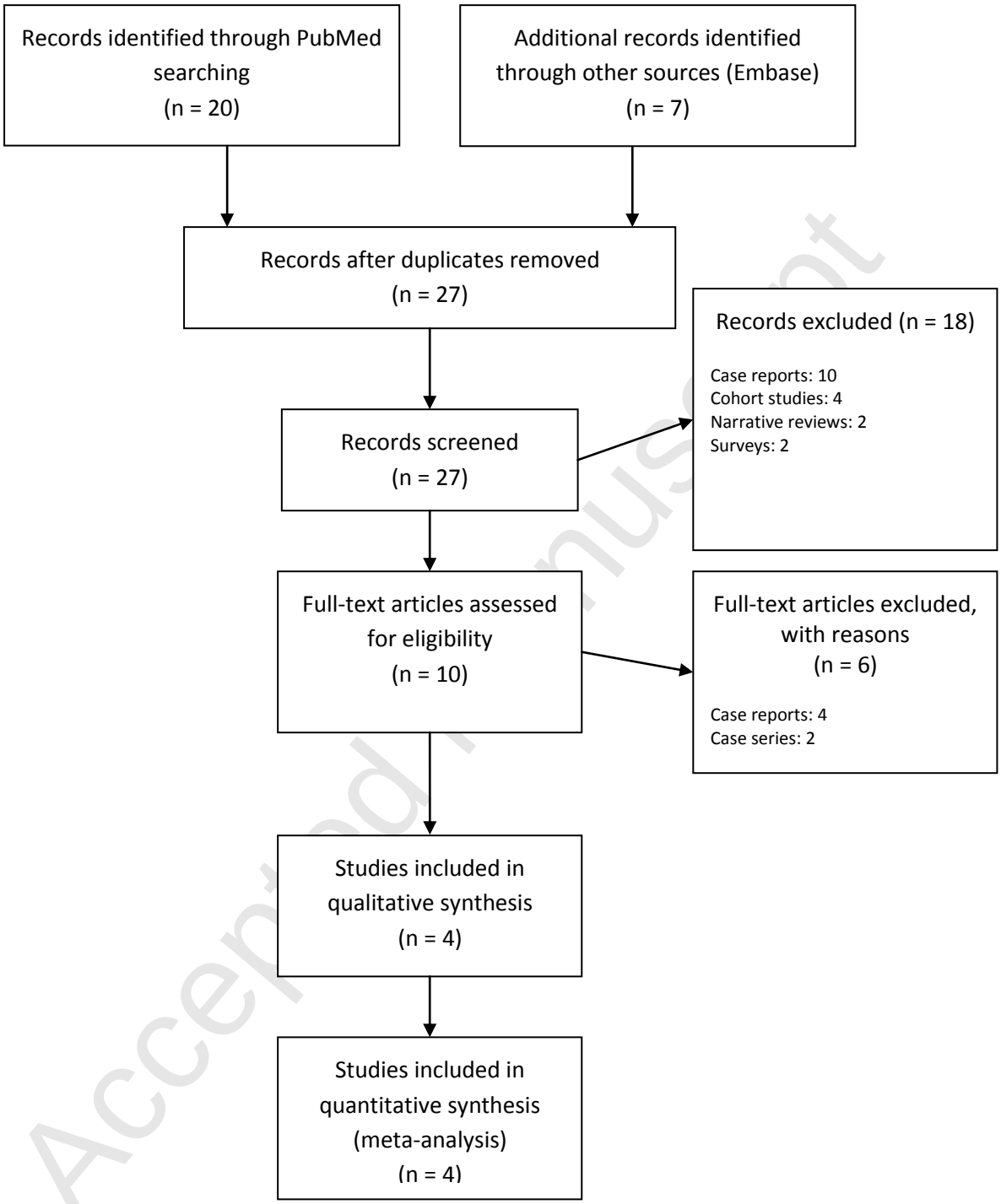


Table 3: Risk of bias assessment of randomized control trial using LMA versus mask ventilation or endotracheal intubation

Study	Study population	Comparison	Main outcomes	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcomes	Incomplete outcome data (attrition and exclusions)	Selective outcome reporting	Source of funding bias
Esmail et al.[72]	GA >35 wks or BW >2500g	LMA (n=20) vs. ETT (n=20)	Apgar scores; Time until heart rate >100/min; LMA and ETT insertion times; rate of successful insertion with 1st attempt; total number of attempts required; duration of PPV;	Uncertain	Uncertain	Uncertain	Uncertain	Low	Low
Singh et al.[73]	GA >35 wks or BW >1500g	LMA (n=25) vs. bag and mask (n=25).	Apgar scores; LMA insertion time; rate of successful insertion with 1st attempt; total number of attempts required; success of ventilation, time required for improvement in color; duration of PPV	Uncertain	Uncertain	Uncertain	Uncertain	Low	Low
Feroze et al.[74]	BW >1500g; APGAR Score <4/10 at birth; Newborns born via C/S	ETT (n=25) vs. BMV (n=25) vs. LMA (n=25)	Apgar scores; LMA and ETT insertion time; rate of successful insertion with 1st attempt; total number of attempts required; success of ventilation, time required for improvement in color;	Uncertain	Uncertain	Uncertain	Uncertain	Low	Low
Zhu et al.[75]	GA >34 wks or BW >2000g	LMA (n=205) vs. bag and mask (n=164)	Apgar scores; LMA insertion time; rate of successful insertion with 1st attempt; total number of attempts required; response time; need for tracheal intubation	High	High	Uncertain	Uncertain	Low	Low

GA - gestational age, BW - birth weight, wks - weeks, g - gram, LMA - laryngeal airway mask, ETT - endotracheal tube, BMV - Bag and Mask Ventilation, C/S caesarian section

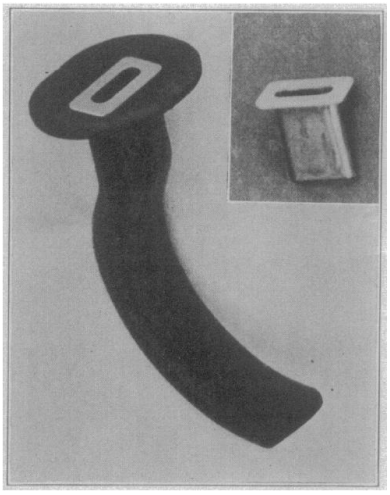
Table 4: Trials identified at clinicaltrials.gov

Study	Study population	Comparison	Primary outcome	Estimated enrollment	Status
Oropharyngeal airway					
Oropharyngeal airway for prevention of airway obstruction during positive pressure ventilation in preterm infants < 34 weeks gestation during neonatal resuscitation[33]	GA <34 wks requiring mask ventilation in the delivery room	Mask ventilation with or without a Guedel Tube.	Reduction in severe airway obstruction	132	Recruiting
Laryngeal mask airway					
Randomized Controlled Trial of Surfactant Delivery Via Laryngeal Mask Airway (LMA) Versus Endotracheal Intubation[35]	GA >29 & >37 weeks with an postnatal age of 4-48 hours	Surfactant administration via LMA vs. ETT (after premedication for pain)	Rate of failure of surfactant therapy	78	Recruiting
Efficacy Evaluation of Surfactant Administration Via Laryngeal Mask Airway[37]	BW >1000g and GA >28 & <35 wks with an postnatal age of <8 hours	Surfactant administration via LMA vs. ETT	Fraction of inspired oxygen	60	Not yet recruiting
Laryngeal Mask Airway (LMA) for Surfactant Administration in Neonates[36]	GA at time of enrollment > 28 & <36 wks with an postnatal age of <38 hours	Infants on nCPAP who receive surfactant via a LMA vs. infants who are maintained on nCPAP and do not receive surfactant.	Need for intubation and mechanical ventilation in the first seven days of life	144	Recruiting
Randomized Controlled Trial of Surfactant Administration by Laryngeal Mask Airway (LMA)[34]	BW >1200g with chronologic age of <72 hours	Infants with RDS who have not yet reached criteria for intubation, will be randomized to receive surfactant by LMA or to continue receiving standard therapy of nCPAP and supplemental oxygen	Rate of failure of surfactant therapy	380 (total of 26 infants were enrolled)	Terminated (due to low enrolment)

GA - gestational age, BW - birth weight, wks - weeks, g - gram, LMA - laryngeal airway mask, ETT - endotracheal tube, nCPAP - Nasal continuous positive airway pressure, RDS - respiratory distress syndrome

Figure 1

A



B

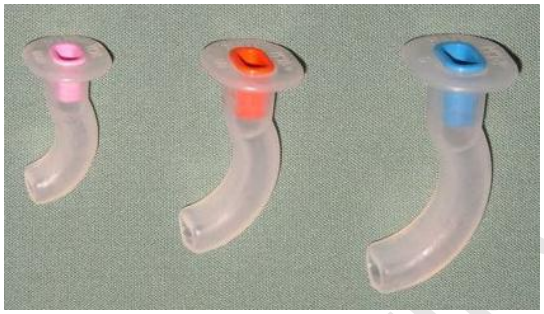


Figure 2

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Esmail 2002	0	20	0	20		Not estimable
Feroze 2008	1	25	0	25	1.5%	3.12 [0.12, 80.39]
Singh 2005	1	25	2	25	6.2%	0.48 [0.04, 5.65]
Zhu 2011	2	205	26	164	92.3%	0.05 [0.01, 0.22]
Total (95% CI)		**275**		**234**	**100.0%**	**0.13 [0.05, 0.34]**
Total events	4		28			

Heterogeneity: $Chi^2 = 6.29$, $df = 2$ ($P = 0.04$); $I^2 = 68\%$

Test for overall effect: $Z = 4.12$ ($P < 0.0001$)