

Surfactant treatment of the meconium aspiration syndrome

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Introduction

Meconium Aspiration Syndrome (MAS) is a disease of term and near-term infants that is still associated with considerable morbidity and mortality. About 5 % of term neonates in Europe are born through meconium stained amniotic fluid. 1 to 2 per 1000 newborn infants develop severe respiratory distress in consequence of MAS. The condition is still far more common in the Middle East, the Indian continent and in Asia (1).

A decrease in both the incidence and the severity of MAS has been observed during the last 20 years in Western countries. This is probably due to improved obstetrical care with better monitoring of the fetus and avoidance of post-term deliveries. Interventions that have been advocated for many years as routine measures like intubation and saline lavage or even the suctioning of meconium stained amniotic fluid from the oropharynx after delivery, have been questioned following negative results of the procedures in large randomised multicenter trials (for review see 2).

During the last decade surfactant administration has become standard for treatment of premature neonates with severe respiratory distress syndrome (RDS). Randomised controlled trials and meta-analyses clearly demonstrate improved gas exchange following surfactant instillation as well as significantly reduced neonatal morbidity and mortality (3). In contrast to RDS that is related to immaturity, MAS and congenital pneumonia can occur in term infants and resemble ARDS in a variety of ways (4-6).

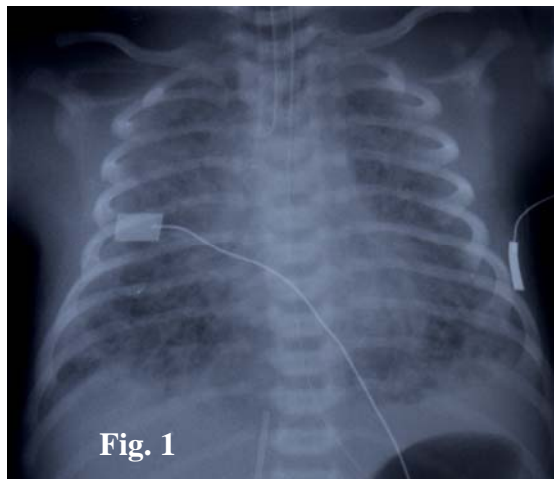


Fig. 1

The chest x-rays of infants suffering from MAS show increased granularity reminiscent of RDS appearance, but also atelectasis and over-inflation (see Fig. 1).

Due to the similarity with RDS, clinical trials using surfactant for MAS have been initiated more than 10 years ago. Still the definitive role of surfactant in MAS is unclear.



Fig. 2

Meconium

Meconium (μήκων, Greek = poppy juice) is a mixture of substances including fetal stool, urine, vernix, hair, epithelial cells and other components of the fetal cavity. Meconium is released into the amniotic fluid during fetal stress/hypoxia. Following pre- or postnatal aspiration, it may then obstruct airways inducing atelectasis and/or overinflation due to its high viscosity (see Fig. 2). Besides from mechanical obstruction, meconium triggers an inflammatory reaction and may contribute to pulmonary hypertension (see Fig. 3).

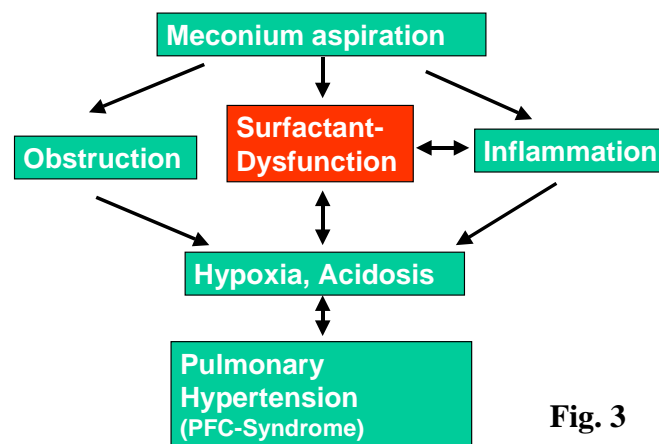


Fig. 3

Meconium and surfactant

Both in vitro experiments and animal work underline the capacity of meconium to interfere with the biophysical activity of surfactant (7, 8). Natural modified surfactants can be inhibited by low concentrations of human meconium (see Fig. 4).

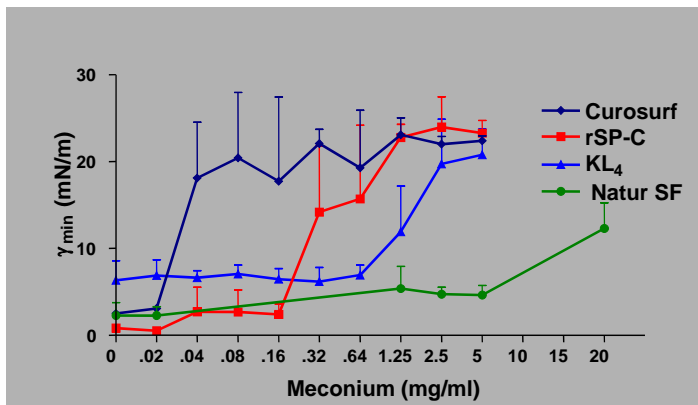


Fig. 4. Minimum surface tension (γ_{\min}) as measured in a pulsating bubble surfactometer following the addition of human pooled meconium. Low surface tension close to zero indicates good biophysical activity.

Modified natural and synthetic or recombinant surfactant preparations are more easy to inhibit than natural lavage surfactant containing all surfactant proteins (modified from ref. 9).

Clinical studies: Surfactant and MAS

Early trials include case reports and smaller retrospective studies showing moderate improvements in gas exchange following surfactant instillation in infants with MAS (10–14). Although repeated doses were used in some of the studies, the response was rather moderate, probably related to the fact that the age of treatment was beyond 12 h of age in many infants.

An important factor for surfactant treatment of MAS seems to be early treatment with high and repeated doses (Fig. 5). The only randomised trial including 20–30 infants per group, demonstrated improved gas exchange following surfactant treatment, when surfactant treatment was initiated before the age of 6 h. None of the infants with MAS died, but there was a lower incidence of air leaks and reduced need for extracorporeal membrane oxygenation (ECMO) in the surfactant treated babies (15).

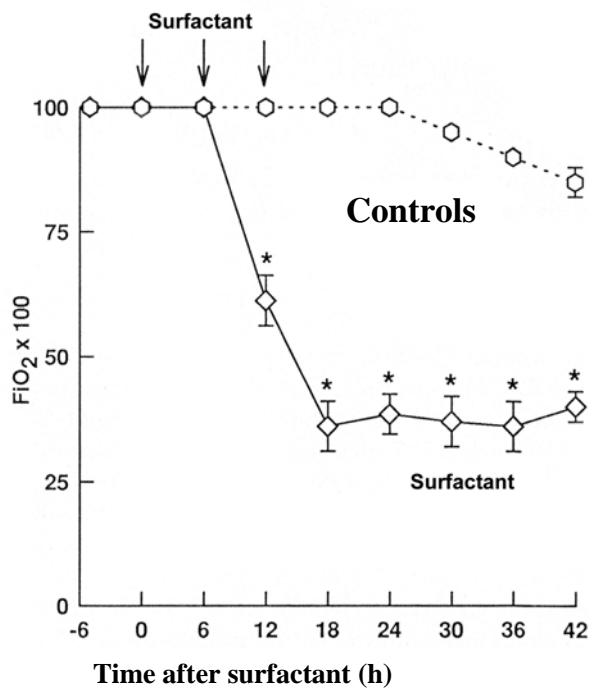


Fig. 5. Randomized controlled trial of surfactant treatment for MAS. 150 mg/kg body weight were administered before the age of 6 h. Up to 4 doses were allowed at 6 h intervals. An improvement in oxygenation was only observed following the second dose, i.e. a cumulative dose of 300 mg/kg body weight. Obviously, the inhibitory potential of meconium has to be overcome, before an effect on oxygenation can be observed (modified from ref. 15).

Although a metaanalysis of all trials of surfactant treatment of MAS (16) demonstrated no benefit in terms of improved survival rates, the lower rate of pneumothorax and the avoidance of ECMO (see Fig. 6) as an invasive procedure may serve as an argument for surfactant treatment. However, the number of ECMO treatments for infants with MAS is constantly decreasing anyhow, as respiratory failure and pulmonary hypertension can often be managed by a combination of surfactant, high frequency oscillatory ventilation (HFOV) and/or inhalation of nitric oxide (NO).



Fig. 6. Term baby with MAS and pulmonary hypertension during the ECMO procedure.

Perspectives

Surfactant inhibition plays an important role in the pathophysiology of MAS. However, the disease is not just the consequence of aspiration of meconium into the airways (17). Many infants with MAS suffer from hypoxia and increased pulmonary vascular resistance already in utero (18–22). This might explain why simply removing meconium by amnioinfusion (23) or postnatal suctioning/intubation (24) has failed to demonstrate effectiveness in randomised controlled trials. Hopefully, better obstetrical monitoring and management can further reduce the incidence of severe MAS.

There is increasing evidence that surfactant improves gas exchange in neonates with severe respiratory failure due to pneumonia and/or MAS. However, larger controlled trials are necessary to determine whether the improved oxygenation can be translated into a better outcome.

Due the presence of surfactant inhibitors in the bronchoalveolar space, larger surfactant doses than those administered for the treatment of RDS seem to be necessary. Studies evaluating surfactant lavage are under way (Fig. 7).

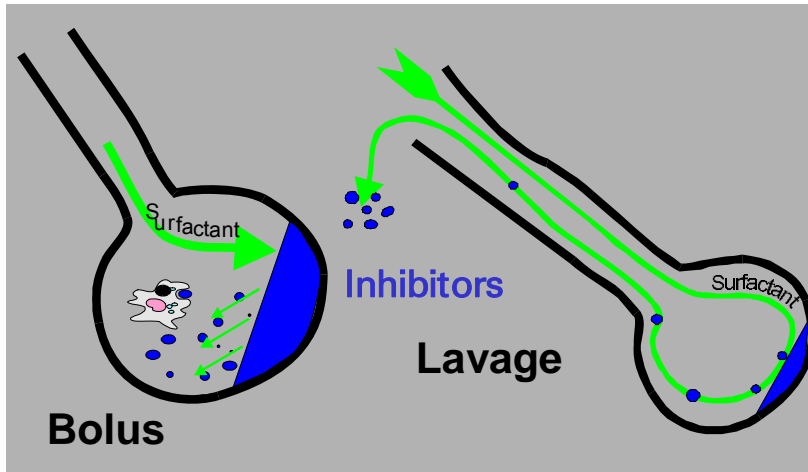


Fig. 7. Schematic drawing: Surfactant as bolus vs. lavage.

In contrast to bolus administration surfactant lavage with diluted surfactant has the theoretical advantage of removing surfactant inhibitors (25, 26). Case reports describe some success with this approach and seem to indicate that lower total doses of surfactant may be effective with the lavage technique (27, 28). However, studies are only available comparing lavage to no surfactant treatment at all and not to the standard bolus technique. In addition, considerable amounts of the lavage fluid remain in the lung and in a recent study lavage had to be stopped in 20-30% of all infants as the procedure was either not tolerated or because of bleeding (29). Therefore, further studies are needed before this approach can be recommended.

Surfactant dysfunction caused e.g. by aspirated meconium can be antagonized by increasing the surfactant concentration. A recent randomised trial from China evaluated 200 mg/kg/body weight surfactant as initial dose and 2 further doses of 100mg/kg at 6-12 h intervals. Again oxygenation was superior in the treatment group, but no significant differences were observed in outcome parameters (30).

In addition, it seems possible to design synthetic surfactants suitable for treatment of ARDS that are more resistant to inactivation (9, 31) e.g. by adding SP-A (32) or polymers like dextran (33, 34). As meconium seems to interfere with the formation of a lipid film on the alveolar surface, cross-linking peptides mimicking the function of e.g. SP-B like polymyxin B (PxB) have also been shown to increase the resistance of surfactant against meconium induced inhibition (35).

Thus future developments might lead to production of surfactant preparations that are safe, available in large quantities and hopefully less expensive as they need not be extracted from animal lungs.

References

1. Dargaville, P., B. Copnell, for the Australian and New Zealand Neonatal Network: The epidemiology of meconium aspiration syndrome: Incidence, risk factors, therapies, and outcome. *Pediatrics* 117 (2006) 1712-1721
2. Wiswell, T. E., P. Srinivasan: Aspiration syndromes. In: Anne Greenough and Anthony D Millner (eds): *Neonatal Respiratory Disorders*. 2nd Edition. 2003, p. 334-354
3. Jobe, A. H.: Pulmonary surfactant therapy. *N Engl J Med* 328 (1993) 861.
4. Ashbaugh, D. G., D. B. Bigelow, T.L. Petty, B.E. Levine: Acute respiratory distress in adults. *Lancet* August 12;2 (1711), (1967) 319-323.
5. Möller, J. C.: Surfactant therapy for acute respiratory distress syndrome. In: Wauer R (ed): *Surfactant Therapy. Basic Principles, Diagnosis*, Georg Thieme Verlag, Stuttgart-New York, 1998, p. 133-145.
6. Ware, L. B., M. A. Matthay: The acute respiratory distress syndrome. *N Eng J Med* 342 (2000) 1334-1349.
7. Moses, D., B. A. Holm, P. Spitale et al.: Inhibition of pulmonary surfactant function by meconium. *Am. J. Obstet. Gynecol.* 164 (1991) 477-481
8. Sun, B., E. Herting, T. Curstedt, B. Robertson: Exogenous surfactant improves lung compliance and oxygenation in adult rats with meconium aspiration. *J. Appl. Physiol.* 77 (1994) 1961-1971
9. Herting, E., P. Rauprich, G. Stichtenoth, G. Walter, J. Johansson, B. Robertson: Resistance of different surfactant preparations to inactivation by meconium. *Pediatr. Res.* 50 (2001) 44-49
10. Auten, R. L., R. H. Notter, J. W. Kendig et al.: Surfactant treatment of full-term newborns with respiratory failure. *Pediatrics* 87 (1991) 101-107
11. Blanke, J. G., G. Jorch: Surfactanttherapie bei 10 Neugeborenen mit Mekoniumaspirations-syndrom. *Klin. Pädiatr.* 205 (1993) 75-78
12. Khammash, H., M. Perlman, J. Wojtulewicz et al.: Surfactant therapy in full-term neonates with severe respiratory failure. *Pediatrics* 92 (1993) 135-139
13. Lotze, A., G. R. Knight, G. R. Martin et al.: Improved pulmonary outcome after exogenous surfactant therapy for respiratory failure in term infants requiring extracorporeal membrane oxygenation. *J. Pediatr.* 122 (1993) 261-268
14. Halliday, H. L., C. P. Speer, B. Robertson: Treatment of severe meconium aspiration syndrome with porcine surfactant. *Eur. J. Pediatr.* 155 (1996) 1047-1051
15. Findlay, R. D., H. W. Taeusch, F. J. Walther: Surfactant replacement therapy for meconium aspiration syndrome. *Pediatrics* 97 (1996) 48-52
16. Soll, R. F., P. Dargaville: Surfactant for meconium aspiration syndrome in full term infants. *Cochrane Database Syst. Rev.* 2000 (2) CD002054
17. Ghidini, A., C. Y. Spong: Severe meconium aspiration syndrome is not caused by aspiration of meconium. *Am. J. Obstet. Gynecol.* 185 (2001) 931 – 938
18. Cleary, G. M., T. E. Wiswell: Meconium-stained amniotic fluid and the meconium aspiration syndrome. *Pediatr. Clin. North Am.* 45 (1998) 511-529
19. Wiswell, T. E., R. C. Bent: Meconium staining and the meconium aspiration syndrome. Unresolved issues. *Pediatric Clinics of North America* 40 (1993) 955-981
20. Wiswell T. E., C. M. Gannon, J. Jacob et al.: Delivery room management of the apparently vigorous meconium-stained neonate: results of the multicenter, international collaborative trial. *Pediatrics* 105 (2000) 1-7
21. Wiswell, T. E.: Advances in the treatment of the meconium aspiration syndrome. *Acta Paediatrica Suppl.* 436 (2001) 28-30
22. Davey, A. M., J. D. Becker, J. M. Davis: Meconium aspiration syndrome: Physiological and inflammatory changes in a newborn piglet model. *Pediatr. Pulmonol.* 16 (1993) 101-108
23. Hofmeyr, G. J.: Amnioinfusion for meconium-stained liquor in labour. *Cochrane Database Syst. Rev.* 1 (2002) CD000014

24. Halliday, H. L.: Endotracheal intubation at birth for preventing morbidity and mortality in vigorous, meconium-stained infants born at term. *Cochrane Database Syst. Rev.* 2000 (2) CD000500
25. Paranka, M.S., W. F. Walsh, B. B. Stancombe: Surfactant lavage in a piglet model of meconium aspiration syndrome. *Pediatr. Res.* 31 (1992) 625-628
26. Herting, E., J. H. Schiffmann, Ch. Roth, S. Zaltash, J. Johansson: Surfactant lavage demonstrates protein fibrils in a neonate with congenital surfactant protein B deficiency. *Am. J. Respir. Crit. Care. Med.* 166 (2002) 1292-1294
27. Lam, B. C., C. Y. Yeung: Surfactant lavage for meconium aspiration syndrome: a pilot study. *Pediatrics* 103 (1999) 1014-1018
28. Wiswell, T. E., G. R. Knight, N. N. Finer, S. M. et al.: A multicenter, randomized, controlled trial comparing Surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. *Pediatrics* 109 (2002) 1081-1087
29. Kattwinkel, J.: Surfactant lavage for meconium aspiration: A word of caution. *Pediatrics* 109 (2002) 1167-1168
30. Chinese Collaborative Study Group for Neonatal Respiratory Diseases: Treatment of severe meconium aspiration syndrome with porcine surfactant: A multicentre, randomized, controlled trial. *Acta Paediatrica* 94 (2005) 896-902
31. Holm, B. A.: Surfactant inactivation in the adult respiratory distress syndrome; in: *Pulmonary surfactant: from molecular biology to clinical practice*; Robertson B., van Golde L. M. G., Batenburg J. J. (eds) Elsevier, Amsterdam 1992, p. 665-684
32. Sun, B., T. Curstedt, G. Lindgren, B. Franzén, A. A. Alaiya, A. Calkovská, B. Robertson: Biophysical and physiological properties of a modified porcine surfactant enriched with surfactant protein A. *Eur. Respir. J.* 10 (1997) 1967-1974
33. Tausch, W., K. L. Lu, J. Goerke, J. Clements: Nonionic polymers reverse inactivation of surfactant by meconium and other substances. *Am. J. Respir. Crit. Care. Med.* 1590 (1999) 1391-1395
34. Ochs, M., M. Schüttler, G. Stichtenoth, E. Herting: Morphological alterations of exogenous surfactant inhibited by meconium can be prevented by dextran. *Resp. Res.* 7 (2006) 86
35. Stichtenoth, G., P. Jung, G. Walter, J. Johansson, B. Robertson, T. Curstedt, E. Herting: Polymyxin B/pulmonary surfactant mixtures have increased resistance to inactivation by meconium and reduce growth of gram-negative bacteria. *Pediatr. Res.* 59 (2006) 407-411