Targeted Early Rescue Surfactant in Ventilated Preterm Infants Using the Click Test

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ABSTRACT. *Objective.* **To determine whether use of the click test, a rapid bedside test of surfactant function, results in earlier and more appropriate surfactant administration in ventilated preterm infants than does usual early rescue treatment.**

Study Design. **Ventilated preterm infants (n = 126) with inspired oxygen ≥25% and mean airway pressure ≥7 cm H_2O were randomized in gestational strata (<28 weeks and 28–36 weeks) to have surfactant therapy determined by the click test or by usual clinical and chest radiograph criteria. The treatment group had the click test performed on a tracheal aspirate as soon as possible after intubation and, if negative or equivocal (surfactant deficient), surfactant was given. The control group had surfactant given as soon as possible based on clinical and chest radiograph diagnoses of respiratory distress syndrome.**

Results. **In infants of <28 weeks' gestation, use of the click test resulted in significantly earlier surfactant therapy (median time: 50 vs 159 minutes) and a reduction in the number of infants receiving surfactant (48% vs 79%). In infants of 28 to 36 weeks' gestation, there was no difference in time to surfactant (median time: 300 vs 268 minutes) or in the number of infants receiving surfactant. Neonatal morbidity and mortality were similar in click test and control groups.**

Conclusions. **Use of the click test in ventilated, extremely premature infants results in significantly earlier and more appropriately targeted administration of surfactant than does early rescue therapy based on clinical and radiograph criteria. A randomized trial of targeted early rescue surfactant therapy versus prophylactic surfactant therapy in infants of <28 weeks' gestation is warranted. The click test has the potential to improve clinical outcomes and reduce costs.** *Pediatrics* **2000;106(3). URL: http://www.pediatrics.org/cgi/content/full/106/3/e30;** ***click test, hyaline membrane disease, infant-premature, surfactant.***

ABBREVIATIONS. RDS, respiratory distress syndrome; APH, antepartum hemorrhage; F_{IO_2}, fraction inspired oxygen; MAP, mean airway pressure; NICU, neonatal intensive care unit.

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Early surfactant therapy has been shown in randomized, controlled trials to improve clinical outcomes of preterm infants with respiratory distress syndrome (RDS).[1–3] The largest study, the OSIRIS trial,[1] reported that in infants of <32 weeks' gestation a reduction in median time to surfactant from 3 to 2 hours resulted in a significant reduction of 16% in the incidence of death or oxygen requirements at the expected date of delivery.

The benefits of early surfactant are also supported by the trials of prophylactic (exogenous surfactant given to all preterm infants at birth) versus rescue surfactant (given to infants after a clinical diagnosis of RDS) in terms of reductions in short-term morbidity and mortality of preterm infants.[4–11] However, between 19% and 68% of infants in the control arms of the trials of prophylactic versus rescue surfactant did not need surfactant. In addition, these trials had low rates of antenatal steroid use (4%–48%, where data are available). With the high rates of antenatal steroid use in current practice, the number of infants who receive unnecessary surfactant is likely to be even greater.

An alternative to prophylactic and standard rescue surfactant therapy is to provide early exogenous surfactant therapy to preterm infants using a rapid bedside test of surfactant function. Tests with the potential to be performed within a short period and with high levels of accuracy are the click test[12,13] and the stable microbubble test.[14–16]

The click test is a rapid, simple bedside test for the diagnosis of surfactant deficiency or inactivation.[12,13,17,18] It may be performed on a variety of specimens including amniotic fluid from pregnant women, the first gastric aspirate, or a tracheal aspirate from newborn infants. When applied to tracheal aspirates, the click test is highly accurate (sensitivity: 93%; specificity: 100%) for the diagnosis of surfactant deficiency, compared with clinical and expert radiologist diagnoses of RDS.[12] This randomized, controlled trial was undertaken to determine whether use of the click test results in earlier and more appropriate surfactant administration in ventilated preterm infants, compared with usual early rescue therapy using clinical and early chest radiograph diagnoses of RDS.

METHODS

Eligibility

Intubated and ventilated neonates were eligible for inclusion if they were born at <37 weeks' gestation and required fraction

inspired oxygen (F_{IO_2}) ≥.25 and mean airway pressure (MAP) ≥7 cm H_2O to obtain an oxygen saturation between 90% and 95%. Infants were excluded if they had a major congenital abnormality, were considered by the attending physician to be unlikely to survive, had previous surfactant therapy, or if their parents refused consent. Outborn infants were eligible for inclusion. The study was approved by the Ethics Committee of Central Sydney Area Health Service.

Allocation

Infants were randomly allocated to treatment or control by use of a computer-generated sequence of numbered, opaque, sealed envelopes in 3 gestational strata (<28, 28–31, and 32–36 weeks). It was unit practice to routinely intubate infants of <28 weeks' gestation, and to intubate infants born at higher gestations if they had severe respiratory distress or required F_{IO_2} ≥.4 oxygen while receiving nasal continuous positive airway pressure.

Interventions

The treatment group had the click test performed on a tracheal aspirate as soon as possible after intubation. If negative or equivocal (surfactant-deficient), surfactant was given before chest radiograph and insertion of lines. The control group received surfactant as soon as possible based on clinical and early chest radiograph diagnoses of RDS. Infants with severe respiratory distress in the control group (F_{IO_2} ≥ .6 and/or peak inspiratory pressure ≥ 25 cm H_2O) were eligible to receive surfactant before a chest radiograph. Further doses of surfactant for both groups were given if clinically indicated (F_{IO_2} ≥ .25 and MAP ≥ 7 cm H_2O). All infants requiring surfactant received a natural surfactant (4 mL/kg of beractant). Infants were ventilated using synchronized intermittent mandatory ventilation, commencing at a rate of 60 bpm, an inspiratory time of .3 seconds, and an end expiratory pressure of 5 cm H_2O to target a partial pressure of arterial oxygen of 60 to 80 and a partial pressure of carbon dioxide in arterial gas of 40 to 50 mm Hg.

A tracheal aspirate was obtained from all infants as soon as possible after intubation and enrolment in the study. Tracheal aspirates from infants in the treatment group were analyzed at the bedside by medical or nursing staff trained in the use of the click test. The methods used to ensure accuracy of the click test have been described previously.[12,18] Training for the click test required staff to receive a demonstration of the test, to perform 30 to 40 tests on a variety of stored samples, and to subsequently demonstrate a high level of agreement with an experienced observer. Infants were defined as surfactant-deficient if the click test was negative or equivocal, and surfactant-sufficient if the click test was positive. Tracheal aspirates from infants in the control group were stored at −20°C and the click test was performed, blind to clinical information, after completion of the study. Reproducibility was checked by storing the residual samples in the click test group at −20°C for reanalysis by 1 observer (D.A.O.) after completion of the study, blind to the result of the initial click test, clinical information, and treatment received.

Performance of the Click Test[12] (Fig 1)

The click test is performed by using a .2-mL sample (tracheal aspirate) placed by autopipette into a glass test tube (12 × 75 mm). The sample is mixed with .2 mL of 95% ethanol, agitated in a vortex mixer (Supermixer, Lab-line Instruments, Melrose Park, IL)

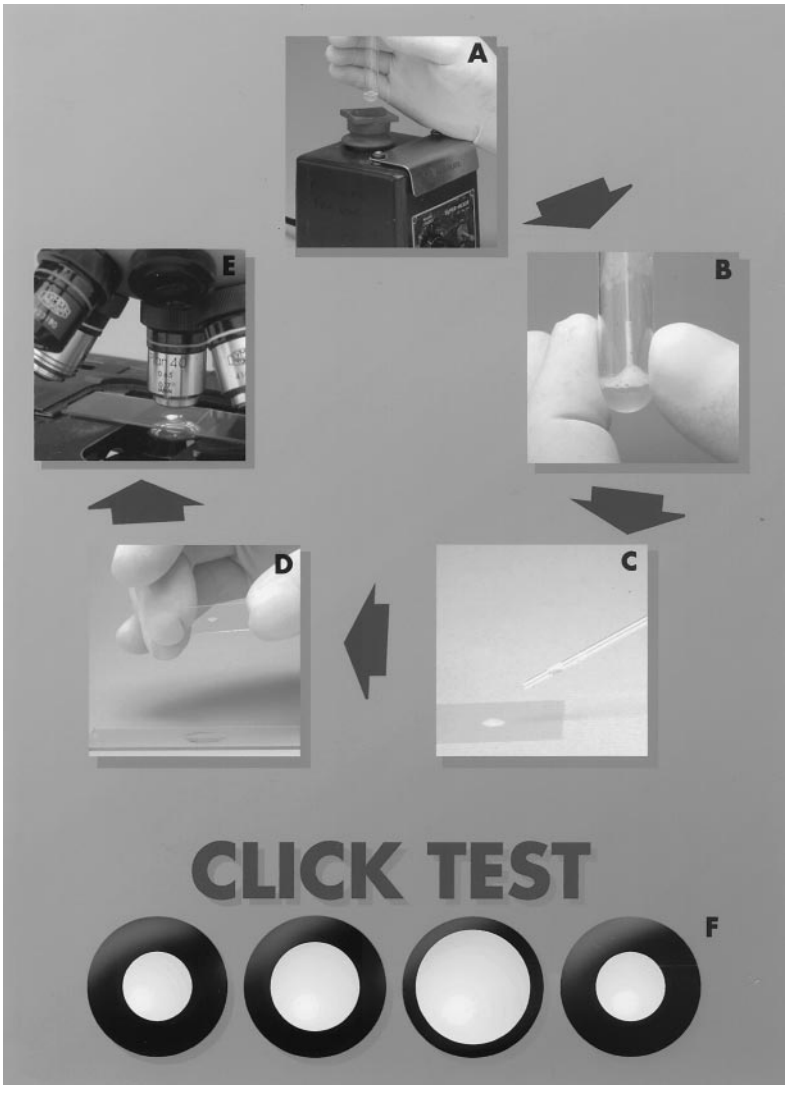

Fig 1. The click test is performed on a specimen of tracheal aspirate taken immediately after intubation of a newborn infant in the following steps. A, Add tracheal aspirate (.2 mL) + 95% ethanol (.2 mL) to test tube and shake in vortex mixer for 15 seconds. B, Pipette bubbles from surface. C, Place bubbles on coverslip. D, Place air-free water into well of glass slide. Drop coverslip to suspend bubbles in air-free water. E, View under × 10 to 40 lens microscope. F, Clicking is the phenomenon where air diffuses rapidly out of bubbles suspended in air-free water. The bubble deforms because of the presence of a surfactant monolayer maintaining the bubble surface area. The white center of the bubble is seen to slowly expand. When a portion of the bubble surface is lost the bubble returns to a spherical shape and the white center is seen to click back to its original size.

for 15 seconds or until bubbles appear. A small sample of bubbles (2–3 drops) is then pipetted off with a Pasteur pipette and placed on a coverslip. One or 2 drops of air-free water are placed into the cavity of the microscope slide (concave cavity: 1.5-cm diameter; Sail brand 15, China Machinery Corporation, Shanghai, China). The coverslip with the bubbles is quickly inverted and placed over the cavity of the microscope slide, allowing the bubbles to hang in the water.

The slide is viewed at 10 to 40 × magnification on a light microscope, and a click is noted when the white center of a bubble is seen to slowly increase in size and then suddenly shrink (click) before increasing again. The test is positive (indicating the presence of active surfactant) when many bubbles are readily seen to be clicking, equivocal when a few (usually <10) bubbles are seen to be clicking after 2 minutes of looking, and negative (indicating the absence of active surfactant) when there are no clicking bubbles to be seen after 2 minutes of searching. Negative and equivocal specimens are repeated immediately to confirm the result, and the result of the slide with the most clicking bubbles is taken to be the true result. If no clicking bubbles are seen, a positive (clicking) control is performed to verify that the air-free water is working.

Bubbles probably click because of the diffusion of air into the surrounding air-free water with resultant deformation of the surfactant-coated bubble and return (click) to normal shape with subsequent loss of surface area.

Outcomes

Primary outcomes included time from birth to first surfactant therapy, use of exogenous surfactant, and major clinical determinants of cost of neonatal intensive care (days intubated, use of rescue therapies such as nitric oxide and oscillatory ventilation, duration of hospitalization, duration of oxygen therapy, and discharge home on oxygen). Secondary outcomes included neonatal mortality, airleak, incidence of intraventricular hemorrhage, chronic lung disease (oxygen at 36 weeks' postmenstrual age), retinopathy of prematurity, and necrotizing enterocolitis.

Statistical Analysis

Before the commencement of this study, the median time to first surfactant treatment of preterm infants in our unit, based on a rescue approach, was 4 hours 15 minutes. It was determined that 124 infants would be required to detect a significant reduction in time to surfactant from 4 to 3 hours at the 5% confidence level with a power of 80%. All data were analyzed using SPSS software (SPSS, Version 7.5 software, Chicago, IL). The χ^2 test and Fisher's exact test were used to detect differences in proportions. The Mann-Whitney *U* test was used to detect differences in median time to surfactant and duration of ventilation, hospitalization, and oxygen therapy. The 2-sample *t* test was used for comparison of parametric continuous variables. The κ statistic was used to document the reproducibility of the click test for samples in the click test group.

RESULTS

Study Participants

Between July 1997 and November 1998, 140 infants of <37 weeks' gestation were admitted to the neonatal intensive care unit (NICU) and ventilated with a maximal FIO_2 ≥.25. One hundred twenty-six infants qualified for inclusion and were recruited to the study. Ten infants did not meet inclusion criteria or were given surfactant before enrolment and 4 were not enrolled because of refused parental consent. Fifty-seven infants were enrolled in the <28 weeks' gestation stratum. The strata, 28 to 31 and 32 to 36 weeks' gestation, had insufficient numbers individually and were combined for all subsequent analyses. Sixty-nine infants of 28 to 36 weeks' gestation were enrolled.

One hundred twenty-six infants were enrolled with 63 infants randomized to each of the click test and control groups. Table 1 compares the characteristics of the click test and control groups. Descriptive variables did not differ significantly between the groups and included mean gestational age, birth weight, growth restriction (birth weight <10th percentile), gender, multiple gestation, use of antenatal steroids, rupture of membranes, maternal antepartum hemorrhage (APH), hypertensive disease of pregnancy, presence of labor, breech presentation, cesarean section, Apgar score at 5 minutes, and proven neonatal infection. There were also no significant differences for any of these variables in the 2 gestational strata (<28 and 28–36 weeks). Fifty-six of the 57 infants of <28 weeks' gestation were intubated before admission to the NICU.

Outcomes

Table 2 compares the outcomes of infants in the combined strata as well as the <28 weeks' and 28 to 36 weeks' gestation strata. In the combined strata, there were no significant differences between control and click test groups for any outcome. There was a trend to reduced use of surfactant (65% vs 78%), median time to surfactant (121 vs 215 minutes), and mortality (8% vs 14%) in the click test group. Causes of the 9 deaths in the control group included respiratory failure with RDS (2), intraventricular hemorrhage (4), necrotizing enterocolitis (2), and cardiac

TABLE 1. Comparison of Clinical Characteristics of Infants in Click Test and Control Groups (No Differences Significant)

Outcome	All Infants			Infants <28 Weeks' Gestation			Infants 28–36 Weeks' Gestation		
	Control *n* (%)	Click Test *n* (%)	*P* Values	Control *n* (%)	Click Test *n* (%)	*P* Values	Control *n* (%)	Click Test *n* (%)	*P* Values
Number	63	63		28	29		35	34	
Gestation (wk; SD)	28.8 (3.5)	28.6 (3.4)	.8	25.7 (1.2)	25.7 (1.1)	.8	31.2 (2.6)	31.2 (2.6)	1.0
Birth weight (g; SD)	1308 (559)	1332 (613)	.8	860 (180)	853 (202)	.9	1667 (497)	1741 (546)	.6
Sex (M/F)	36/27	34/29	.7	14/14	12/17	.5	22/13	22/12	.9
Any steroids	54 (86)	54 (86)	1.0	26 (93)	27 (93)	1.0	28 (80)	27 (79)	1.0
Rupture membranes >24 h	12 (19)	12 (19)	1.0	8 (29)	8 (28)	.9	4 (11)	4 (12)	1.0
APH	18 (29)	17 (27)	.8	9 (32)	10 (34)	.9	9 (26)	7 (21)	.3
Hypertensive disease	11 (17)	14 (22)	.5	2 (7)	5 (17)	.4	9 (26)	9 (26)	.9
Labor	40 (63)	37 (59)	.6	22 (79)	22 (76)	.8	18 (51)	15 (44)	.5
Cesarean section	39 (62)	33 (52)	.3	13 (46)	13 (45)	.9	26 (74)	20 (59)	.2
Median 5-min Apgar (range)	8 (1–10)	8 (4–10)	.3	8 (3–10)	8 (4–10)	1.0	8 (1–10)	9 (5–10)	.2

SD indicates standard deviation

TABLE 2. Comparison of Outcomes of Infants in Click Test and Control Groups

Outcome	All Infants			Infants <28 Weeks			Infants 28 to 36 Weeks		
	Control *n* (%)	Click Test *n* (%)	*P* Values	Control *n* (%)	Click Test *n* (%)	*P* Values	Control *n* (%)	Click Test *n* (%)	*P* Values
Number	63	63		28	29		35	34	
Surfactant therapy									
Surfactant	49 (78)	41 (65)	.1	22 (79)	14 (48)	.02*	27 (77)	27 (79)	.8
Median time	215 min	121 min	.2	159 min	50 min	.002*	268 min	300 min	.7
Surfactant dose			.2			.04*			.9
None	14	22		6	15		8	7	
1	26	19		10	4		16	15	
2	23	22		12	10		11	12	
Neonatal morbidity									
Died	9 (14)	5 (8)	.3	5 (18)	4 (14)	.7	4 (11)	1 (3)	.4
Pneumothorax	1 (2)	0 (0)	1.0	1 (4)	0 (0)	.5	0 (0)	0 (0)	
Postnatal steroids	20 (32)	14 (22)	.2	17 (61)	13 (45)	.2	3 (9)	1 (3)	.6
Days intubated (median)	5.0	4.0	.3	11	5	.4	3	3	.7
Days in oxygen (median)	7.0	7.0	.9	50	35	.6	3	4	.9
Oxygen at 36 wk	15 (28)	14 (24)	.7	13 (57)	11 (44)	.4	2 (6)	3 (9)	1.0
Intraventricular hemorrhage (all)	12 (20)	11 (19)	.9	9 (32)	9 (31)	.9	3 (10)	2 (7)	.4
Retinopathy (all)	17 (41)	14 (32)	.4	13 (57)	12 (46)	.5	4 (22)	2 (11)	.7
Days in hospital (median)	57	60	.5	83	77	1.0	35	37	.6

* Significant $P < .05$.

tamponade from long line extravasation postsurgery for a tracheo-esophageal fistula (1). Causes of the 5 deaths in the click test group included respiratory failure with RDS (1), intraventricular hemorrhage (2), hypoxic–ischemic encephalopathy (1), and chronic lung disease (1).

A significant decrease in the use of surfactant (48% vs 79%; $P = .02$) and a reduction in median time to surfactant (50 vs 159 minutes; $P = .002$) were seen in the click test group in infants of <28 weeks' gestation. Figure 2 represents a box plot of times to first surfactant for click test and control groups for infants of <28 weeks' gestation. Similar numbers of infants in both groups required 2 doses of surfactant. However, fewer infants in the click test group received 1 dose, with more avoiding surfactant altogether ($P = .04$). There was no significant difference in mortality, respiratory morbidity (pulmonary hemorrhage, pneumothorax, use of postnatal steroids, duration of intubation, duration in oxygen, and incidence of chronic lung disease), use of rescue therapies, incidence of intraventricular hemorrhage or retinopathy, and duration of hospitalization.

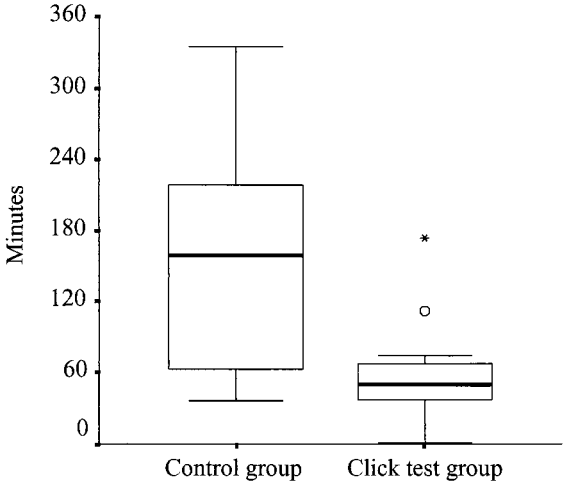

Fig 2. Median time to surfactant for infants <28 weeks' gestation in the control and click test groups (159 vs 50 minutes; $P = .002$). Median times are indicated by central band; box represents the interquartile range, with whiskers extending up to 1.5 interquartile range from the upper and lower limits of the box. Circles and crosses represent outliers.

For infants of 28 to 36 weeks' gestation, there was no difference in the use of surfactant, median times to surfactant, or any other outcome variable as documented in Table 2. An appreciable clinical delay was seen in surfactant treatment for both control and click test groups (median time: 268 vs 300 minutes). A delay in intubation in excess of 1 hour from birth was seen in 34 of 69 of the preterm infants (49%) of 28 to 36 weeks' gestation. The median time of intubation of these 34 infants was 5 hours (range: 2–42 hours), with a median FIO_2 before intubation of .45 (range: .3–1.0).

In the click test group, 4 of 25 infants with a positive click test (surfactant sufficient) were subsequently given surfactant (Table 3). No clear clinical pattern could be seen in these infants. Primary indications for delivery in these 4 infants included preterm rupture of membranes with group B streptococcus colonization, preeclampsia (with cord acidosis), APH, and idiopathic preterm labor. One infant in the click test group who met enrolment criteria was rapidly weaned to air but had a negative click test. This was found to be attributable to a problem with the reagents. The infant was not given surfactant. In the control group, 16 infants received surfactant who were subsequently shown to be click test-positive (Table 3). Five of the 16 infants were delivered after an APH or abruption, 5 infants had evidence of fetal distress (2 with APH) as evidenced by low cord pH or cord base deficit, and 3 were delivered after prolonged rupture of membranes. Five infants were delivered after uneventful preterm labor.

Sixty-two of 63 specimens from the click test group were available for reanalysis after storage at −20°C

TABLE 3. Correlation Between Click Test and Surfactant Treatment or Repeat Click Test in Click Test and Control Groups

Treatment Group: Result of Initial Click Test and Use of Surfactant in the Click Test Group	Surfactant Given		Total
	No	Yes	
Click test			
Negative	1	37	38
Positive	21	4	25
Total	22	41	63

Control Group: Result of Delayed/Blinded Click Test Result According to Original Surfactant Treatment for Controls	Surfactant Given		Total
	No	Yes	
Click test			
Negative	2	31	33
Positive	12	16	28
Total	14	47	61

Treatment Group: Repeatability of Click Test in the Click Test Group	Repeat Click Test		Total
	Negative	Positive	
Initial click test			
Negative	36	1	37
Positive	3	22	25
Total	39	23	62

κ = .86 (95% confidence interval: .73–.99).
Note: Click test-negative = surfactant-deficient; click test-positive = surfactant-sufficient.

(Table 3). Reproducibility was 93% with a κ of .86 (95% confidence interval: .73–.99). Sixty-one of 63 control specimens were available for delayed analysis (Table 3).

DISCUSSION

The click test has been shown to have a high level of accuracy when applied to tracheal aspirates from preterm infants.[12] The accuracy compares favorably with other tests of surfactant performed on tracheal aspirates, including the stable microbubble test,[14–16] the shake test,[12,13] lecithin/sphingomyelin ratios,[19,20] and phosphatidylglycerol levels.[21,22] The click test has also been shown to have a high level of interobserver reliability (κ = .74).[18] This pragmatic trial demonstrates the efficacy of using the click test in a realistic clinical setting.

Infants <28 Weeks' Gestation

This study demonstrates that use of the click test in ventilated, extremely preterm infants (<28 weeks' gestation) has the potential to significantly reduce the time to first surfactant therapy, compared with rescue therapy based on clinical and early chest radiograph diagnoses of RDS. Several trials of rescue surfactant therapy have demonstrated the benefits of early surfactant treatment.[1–3] The reduction in median time to surfactant for all infants <37 weeks' gestation to 121 minutes represents a 53% reduction from the pretrial audit and a 44% reduction compared with controls. The benefits were almost exclusively seen for infants of <28 weeks' gestation who were nearly always intubated before admission. An early tracheal aspirate and click test can be performed within 10 to 15 minutes of admission to the NICU and surfactant therapy can be targeted to those infants with an immature surfactant test.

Use of the click test in ventilated infants of <28 weeks' gestation resulted in a 39% reduction in use of surfactant, compared with rescue therapy based on clinical and early chest radiograph diagnoses of RDS. Similar numbers of infants received 2 doses of surfactant suggesting that the click test correctly identified those infants with significant RDS. Fewer infants in the click test group received only a single dose of surfactant, instead avoiding unnecessary surfactant altogether. There was no evidence of any harm from the reduction in use of surfactant in this trial, with similar morbidity and mortality in both groups. Respiratory morbidity was similar with 3 infants of <28 weeks' gestation dying from early respiratory failure, 2 of whom were in the control group. Trends to benefit in terms of duration of mechanical ventilation, duration of oxygen therapy, and incidence of chronic lung disease favored the click test group. Although this trial was not of sufficient size to have the power to detect clinically important improvements in these respiratory outcomes, the literature adequately documents the benefits of early surfactant in these infants.[1–3]

An alternative to targeted early rescue therapy using a bedside test of surfactant is to give all preterm infants at risk of RDS surfactant at birth (surfactant prophylaxis). The benefits of early surfactant are supported by the trials of prophylactic versus rescue surfactant in terms of reductions in short-term morbidity and mortality of preterm infants.[4–11] Several problems exist in interpreting the results of these trials. First, rescue therapy was suboptimal by today's standards. Second, many infants in the control arms of the trials of prophylactic versus rescue surfactant did not need surfactant. In addition, trials where data are available had low rates of antenatal steroid use. Given the high rates of antenatal steroid use in current practice, the number of infants who receive unnecessary surfactant is likely to be even greater. In the current trial, 93% of infants of <28 weeks' gestation had the benefit of some antenatal steroids and 68% of infants had a completed course. As a result, 52% of infants were found to be surfactant-sufficient and avoided unnecessary surfactant in the click test arm of the trial.

A large trial of 2 different strategies for surfactant prophylaxis failed to show any benefit from an immediate dose of surfactant postdelivery, compared with a strategy of early postventilatory surfactant.[23] Infants who received postventilatory surfactant had usual resuscitation performed and surfactant given after 10 minutes of age. There was no difference in mortality and a significant reduction in chronic lung disease (at 36 weeks' corrected age) in the postventilatory group. It is feasible to perform the click test on all ventilated, extremely premature infants within 10 to 15 minutes of birth. A delay in median time to surfactant therapy from birth of 50 minutes in the

click test group for infants of <28 weeks' gestation was contributed to by the enrollment of exutero transfers and a delay in meeting eligibility criteria. Because there seems to be no benefit to immediate (preventilatory) surfactant therapy, a policy of early, targeted surfactant therapy using the click test would result in at least 50% of infants born extremely prematurely avoiding unnecessary surfactant therapy and receiving surfactant at an appropriately early time. A trial of early targeted surfactant therapy (using a test of surfactant function) versus prophylactic surfactant therapy is now warranted. With 760 live births between 24 and 27 weeks' gestation in Australia,[24] use of the click test has the potential to save approximately US $137 000 per year in unnecessary surfactant costs in Australia.

Infants >27 Weeks' Gestation

The benefits from use of the click test were not seen in higher gestation infants (28–36 weeks'). There was a considerable delay in surfactant therapy in both click test and control groups, largely attributable to a delay in meeting criteria for intubation. Unit policy meant that infants were not intubated until they reached 40% oxygen in the first 24 hours while on continuous positive airway pressure. Although the click test may be performed on the first gastric aspirates of nonintubated newborn infants to diagnose surfactant status, it is less accurate with a positive and negative predictive value of 73% and 97%, respectively (specificity: 84%; sensitivity: 95%).[12] Verder et al[3,25] have shown that a strategy of low versus high threshold for intubation and surfactant therapy improved oxygenation and reduced the subsequent need for intubation in preterm infants of <30 weeks' gestation. This was despite initial intubation of 50% more infants than would otherwise have been intubated. There are currently no data to suggest up to what gestation a strategy of early intubation for surfactant therapy may be extrapolated. Data from our unit would indicate that even at 34 to 36 weeks' gestation, 50% of infants who reach a F_{IO_2} ≥.3 subsequently are intubated and receive surfactant; similar numbers to those in the studies by Verder et al.[3,25] A trial of low threshold for intubation and surfactant therapy as determined by the click test is needed in infants of >30 weeks' gestation.

CONCLUSION

Use of the click test in ventilated, extremely preterm infants results in significantly earlier and more appropriately targeted administration of surfactant than does early rescue therapy based on clinical and radiograph criteria. A trial of early targeted surfactant therapy (using a test of surfactant function) versus prophylactic surfactant therapy is now warranted. Use of the click test has the potential to improve clinical outcomes and reduce costs. Further studies are needed to target larger preterm infants for earlier intubation and surfactant therapy.

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