Acta Biomed 2015; Vol. 86, Supplement 1: 16-20

Original article

German experience in the management of ELGAN infants

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Summary. Of 680 000 infants born in Germany a year roughly 10% are preterm and 1% are very preterm. They are treated in around 150 level 1 perinatal centers and there are various credos how to best treat the ELGAN infant. However, many centers include the use of a sustained inflation for lung aeration in the standard protocol of delivery room care in Germany. As a result of the large studies on delivery room care, a trend for earlier or prophylactic surfactant in the most immature infants can be observed, however, surfactant is increasingly given in a new less invasive way called LISA. German randomized controlled trials on LISA , on permissive hypercapnia in the premature infants and a German initiated European trial on inhaled steroids have been completed and preliminary results are available. NIRS so far mostly is used for research reasons; however, the number of centers that monitor brain oxygenation for clinical reasons to guide hemodynamic management is increasing. A recent initiative was able to tremendously reduce the rate of IVH by prospective multidisciplinary surveillance. (www.actabiomedica.it)

Key words: surfactant, sustained lung inflation

Introduction

Survival of ELGA newborns (ELGAN) has increased notably over the past years, however, rates of long term sequel like bronchopulmonary dysplasia and neurologic impairment have not improved satisfyingly. Optimal respiratory and cardiovascular management in the very first hours and days of life is the mainstay to avoid such complications. However, despite the growing number of large trials there is still lack of knowledge about the best approach for the individual infant. Evidence and clinical experience have to be merged for a better outcome. Various approaches have been tested in Germany in the recent years:

Delivery room (DR) care:

In the early nineties the application of a sustained inflation to facilitate the adaptation to postnatal life was introduced into German neonatal units empirically by Wolfgang Lindner and Frank Pohlandt from Ulm (1,2). It was not until ten years later, that the rationale and benefit of this approach was studied in more detail. Prenatally the lung of the fetus is filled with lung fluid causing a high resistance of the newborns airways. te Pas et al. were able to visualize in the premature rabbit model that a long lasting inflation of more than 10 seconds is able to move the water column into the peripheral parts of the lungs, from where it is taken up into the lung interstitium (3,4). The resulting high functional residual capacity, the proposed homogenous lung aeration and the lower systemic inflammatory response compared to single breaths lung aeration in this animal model is attractive. Indeed a recent Italian study was able to proof a lower need for intubation after sustained inflation (5) and almost 30% German centers have adopted this policy (6-8). Furthermore, sustained inflations are easy to apply and effective in stabilization the infant in the DR. However, secondary outcomes from the above study, and retrospective data from a single center associate air leaks with the application of sustained inflation, therefore, caution

using this procedure may be advised (5,9). Sustained inflations are currently tested in a large international trial (SAIL-trial) (10).

Indication of surfactant therapy and/or invasive ventilation

Avoidance of mechanical ventilation by the use of early noninvasive support was a mainstay in the support of ELGANs in Germany. However, large scale international delivery room randomized controlled trials failed to identify significant benefits of this approach compared to the classical approach with intubation in the DR (11-14). Unexpectedly, a somewhat higher incidence of airleaks was observed with the noninvasive approach, especially if high thresholds for intubation were applied (11). Likely, this results from negative effects of late surfactant therapy in the course of moderate to severe surfactant deficiency. Would it be more advantages to treat all infants with surfactant very early? Prophylactic surfactant therapy translated not into better outcomes (15). Some infants will not need surfactant therapy and may be treated unnecessarily. Most infants with early CPAP success without surfactant require very little or no additional oxygen for respiration (8). Identification of infants in need of surfactant identified at low FiO2 thresholds (0.3-0.4) and treatment without delay as soon as certain thresholds are met may be a key strategy to optimize respiratory outcomes.

Mode of surfactant application

The classic approach to deliver surfactant is intubation and surfactant therapy followed by mechanical ventilation. Attempts to deliver surfactant noninvasively by inhalation (16) or via the pharynx were hampered by low surfactant deposition. The high lipid/phospholipids content impedes nebulization. Angela Kribs from Cologne introduced in 2003 a new method to deliver surfactant through a very thin gastric tube into the trachea during spontaneous breathing (17). This approach which is now called LISA (Less Invasive Surfactant Application) recently was tested in three randomized controlled trials (RCT)s. The AVM trial in infants 26-28 weeks GA showed shorter duration of mechanical ventilation and less oxygen demands at age 28 days, however no benefit in mortality or rate of bronchopulmonary dysplasia (BPD) (18). The Take Care study compared surfactant therapy by INSURE (Intubation, Surfactant, Extubation) and LISA (19). The need for mechanical ventilation in the first 72 hours of life and the rate of BPD was significantly lower in the LISA group when compared with the InSurE group. The NINSAPP trial tested if this form of surfactant delivery is suitable for very premature infants. Infants of 23 + 0/7 to 26 + 6/7 weeks GA were randomized to LISA or surfactant therapy followed by mechanical ventilation. No difference in death or rate of BPD was found, however, the rate of intraventricular hemorrhage (IVH) was lower in the LISA group ((20) Tab. 1). LISA may in future proof to be non inferior or even superior to the classical surfactant application. Despite the sparse safety data being available, LISA is increasingly used in Germany. Data from the German neonatal network have recently been published. Between 2009 and 2012, 1103 infants <32 weeks have been treated with LISA in the network. Compared to matched controls rates of BPD, mechanical ventilation but not IVH were decreased (21).

Gentle ventilation

Despite new noninvasive modes to deliver surfactant up to 50% of infants may finally require invasive ventilation. Therefore, techniques to avoid ventilator induced lung injury are mandatory, if low rates of chronic lung disease or death are wanted. A potential strategy to decrease ventilatory needs and by this attenuate lung injury is to allow for a moderate level of hypercapnia. Ulrich Thome from Leibzig recently performed a German multicenter randomized controlled trial in preterm infants of 23-28 weeks GA to study the effects of permissive hypercapnia in ELGANs who

Table 1. NINSAPP trial (20)

	Control (n=104)	Lisa (n=107)	p-value
Death	12 (12)	10 (9)	0.59
BPD	31 (30)	25 (23)	0.34
IVH	41 (39)	26 (24)	0.017
IVH>II°	23 (22)	11 (10)	0.019

Table 2. Phelbi Trial (22); interims analysis

	Permissive Hyperkapnia (n=156)	Control (n=156)	p-value
BPD or Death	57 (38%)	51 (35%)	n.s.
IVH	53 (34%)	55 (36%)	n.s.
IVH3-4	21 (14%)	15 (10%)	n.s.

Table 3. Neurosis Trial (24)

	Control (n=419)	Budesonide (n=437)	p-value
BPD or Death	194 (46.3%)	175 (40%)	0.053
Death	57 (13.6%)	74 (16.9%)	-
Survival with BPD	138/363 (38%)	101/363 (27.8%)	-

required intubation and ventilation. A PCO2 of 55-65 mm Hg was targeted in the permissive hypercapnia group and compared to 40-50 mm Hg in the standard group. In both groups pCO2 increased in steps by 5 mm HG after the fourth day. 359 infants of 23 + 0/7 to 27 + 6/7 weeks GA were included before the trial was stopped early because of futility. Preliminary results of the interims analysis have recently been published (22, Table 2): No difference in the rate of BPD and death (36% vs 30%) were found. The rates of IVH were similar. Therefore, increasing the PCO2 targets may not be helpful and lung protective in the majority of infants. However, allowing for some more moderate degree of hypercapnia in cases of severe lung disease seems to be tolerated well without affecting the rate of intraventricular hemorrhage or other outcomes.

Inhalative steroid treatment

Early postnatal steroids attenuate lung inflammation, improve pulmonary function, facilitate extubation and decrease the rate of BPD and/or death. However, systemic steroids have been linked to adverse neurologic outcome. Therefore, high dose steroid therapy of the preterm infant needs to be restricted to the sickest infants in very severe respiratory distress. Dirk Bassler from Tübingen addressed in his large scale European randomized trial (NEUROSIS) the question, if inhaled steroids may prevent chronic lung disease without affecting neurologic outcome negatively. Infants 23 + 0/7 to 27 + 6/7 were randomized to inhalative budesonide or placebo within the first 12 h of life and continued as long as additional oxygen was necessary. Preliminary results have recently been published (23;24). Inhalation of steroids significantly reduced the rate of BPD (Table 3). However, the effect was very modest and the rate of BPD or death was reduced by 6% only. Inhalation of steroids may not be the magic bullet to improve long term respiratory outcome.

Near infrared spectroscopy in the delivery room

Studies from Ulm (25) and Graz (26,27) describe the use of near infrared spectroscopy to assess regional cerebral oxygenation in the delivery room. Knowledge of the regional organ oxygenation may help to monitor adequate oxygen supply of the newborns brain which relies on arterial oxygenation, and oxygen carriers, but also on cerebral perfusion and cerebral metabolism. Percentiles of oxygen cerebral oxygenation during transition have been described in preterm and term infants. Some infants that later developed IVH had low cerebral oxygenation during and after delivery room care despite an arterial oxygen saturation within normal limits. Therefore, low cerebral blood flow very early in postnatal life may cause low tissue oxygenation which may precede IVH. Gorm Greisen from Copenhagen tested in a multicenter pilot RCT in 166 infants <28 weeks GA if cerebral oxygenation can be held within certain target ranges (55-85%) by adjusting various factors i.e. FiO2, cardiac output or hematocrit (28). Cerebral oxygenation (primary outcome) was outside the recommended range for 36.1 (9.2-79.5%) % hours compared with 81.3 (38.5-181.3) % hours in the control group. Most exiting was the fact that brain damage (secondary outcome) was strikingly lower in the NIRS group (13 vs 23% severe brain injury). Interestingly >80% of actions taken to correct cerebral oxygenation was adjustment of FiO_2. NIRS, therefore, may in future help to improve outcomes and lowering the rate of IVH.

Intraventricular hemorrhage

Intraventricular hemorrhage is a major threat and the main risk factor for adverse neurologic outcome. It

Table 4. Surveillance to reduce IVH (29)

	Rate of severe IVH prior to intervention N=263	Rate of severe IVH after intervention N=191
<24 weeks GA	26.9%	15.4%
24–25 SSW	18.3%	6.3%
26–27 SSW	8.3%	4.2%
28–29 SSW	0%	0%
Total	9.1%	3.7%

affects foremost the extremely immature and sickest preterm infants. Various risk factors like immaturity, low blood pressure, sepsis have been associated with IVH, however, very little therapeutic options have arisen from this knowledge. Helmut Hummler from Ulm recently introduced an effective approach to lower rates of IVH (29). In this IVH initiative in the first step risk factors for IVH were identified by literature research. Furthermore, centers with known low rates of IVH were visited to identify potentially better practices. From this a bundle of practices were identified. Examples of these practices included: late cord clamping, no allowance of hypotension for >1h, early surfactant therapy without any delay, normocapnia, strict minimal handling policy. Adherence to these practices was henceforward in detail prospectively monitored for any preterm infant. Furthermore, each clinical course was discussed in an interdisciplinary conference of neonatologists, obstetrician and nurses on a weekly base. As a consequence overall rates of IVH decreased in infants <1500g birth weight from 22% to 10%, in infants <1000 g from 29% to 15% and in preterm infants <28 weeks from 34 to 16% (Table 4). None of the identified practices was new: It seems rather that the most important factor for the observed decrease in IVH rate was the multidisciplinary and standardized approach in addition to high guideline adherence as a result of the continuous surveillance.

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