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Morbidity and mortality trends in very–very low birth weight premature infants in light of recent changes in obstetric care

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ABSTRACT

Objective: In this study, we describe trends in morbidity and mortality of preterm infants with less than 500 mg birth weight in the changing landscape of obstetric and neonatal care.
Study design: During a ten year study period between 2006 and 2016 we assessed outcome data for all neonates with less than 500 mg birth weight born at our Neonatal Intensive Care Unit. We divided study subjects into two groups based on whether their birth date fell in the first half (2006–2010; n = 39) versus the second half (2011–2015; n = 27) of the study period comparing clinical outcomes in the two groups. We also assessed several clinical parameters for association with postnatal survival by comparing relative frequencies for each clinical parameter among surviving infants versus mortality cases.
Results: Survival rate for preterm neonates with less than 500 mg birth weight born between 2006 and 2010 was 30.8%. This survival rate rose to 70.4% in the second half of the study period between 2011 and 2015 ($p < 0.05$). Among surviving babies premature birth was found to be predominantly associated with maternal hypertension or intrauterine growth restriction while in those who died premature birth due to premature rupture of membranes and spontaneous preterm labor were significantly more common. All surviving infants with less than 500 mg birth weight were born via cesarean section whereas among those who died cesarean section had been performed in only 80% and vaginal delivery in 20% representing a significant difference between the groups ($p < 0.05$). The majority (90.3%) of surviving infants with less than 500 mg birth weight had received surfactant therapy while the proportion of neonates receiving surfactant therapy among mortality cases was significantly lower (65.2%; $p < 0.05$).
Discussion: Our findings suggest that among premature neonates with less than 500 mg birth weight preterm delivery due to premature rupture of membranes and intrauterine infections represents the worse mortality risk. Steroid prophylaxis and measures to prevent and treat intrauterine infections with appropriate use of antibiotics can markedly improve survival in these cases. In premature neonates with less than 500 mg birth weight survival is more favorable after cesarean section compared to vaginal delivery.

Introduction

Premature delivery is defined as birth before 37th week of gestation. The majority of preterm deliveries take place between gestational weeks 24–37. The etiology is multifactorial; it is associated with the general level of healthcare, the quality of obstetric care and several gestational and maternal factors including maternal age, presence of multiple pregnancy, nutrition, smoking and multiple other obstetric or medical conditions developing during gestation [1].

Low birth weight is defined as neonatal weight less than 2500 g at birth. Low birth weight is commonly associated with either premature birth or intrauterine growth restriction (IUGR). The delivery of an infant with higher than 500 g birth weight showing life signs is considered life birth independent of gestational age calculated by Naegele's formula. Rarely, a live infant with less than 500 g birth weight may be delivered even after the 24th gestational week [2].

In general, morbidity and mortality of infants delivered prematurely may markedly exceed morbidity and mortality of

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those born on term. Specifically, neonates born with extremely low birth weight are prone to develop a variety of both short-term and long-term postnatal medical conditions. Short-term conditions include e.g. idiopathic respiratory distress syndrome (IRDS), bronchopulmonary dysplasia (BPD) or necrotizing enterocolitis (NEC) [3], while long-term sequalae may include respiratory disorders including bronchial asthma, growth retardation, short-bowel syndrome or cerebral palsy [2,4–6].

Overall, both low birth weight and low gestational age at delivery can be considered as some of the strongest predictors for postnatal clinical outcomes in premature infants [7,8].

Data from the US shows that in 2009 out of a total of 4.1 million life births 0.17% had a less than 500 g birth weight. The postnatal mortality for these cases reached 83.4% [8]. In Hungary, birth rate for preterm infants with less than 500 g birth weight is reported as 35–40 cases per annum with a postnatal mortality rate of approximately 80% [9]. Among the survivors developmental disorders of the central nervous system represent the predominant long-term morbidity [10].

In the last few decades there has been a major improvement in both postnatal morbidity and survival rate of premature infants. This success has been even more marked in the case of neonates born with less than 500 g birth weight [4–6].

Caring for neonates with less than 500 g birth weight is a major challenge both professionally and in terms of ethical considerations [11]. We simply do not have standard recommendations and international guidelines on acute care or resuscitation decisions for neonates born with very low gestational age or birth weight [12]. Although traditionally only neonates born after the 24th gestational week or weighing at least 500 g at birth had been considered candidates for active care in the neonatal intensive care unit, there is now a worldwide consensus to resuscitate and actively treat every newborn baby showing any life signs [13,14].

We undertook to study clinical predictors of postnatal morbidity and mortality of premature infants with less than 500 g birth weight born at our institution in the past ten years between 2006 and 2015. We compared clinical characteristics of surviving infants to those who subsequently died in an attempt to identify clinical predictors of mortality; at the same time we assessed changes in clinical outcomes during the first half versus the second half of the study period to describe temporal trends in morbidity and mortality. We hypothesized that improvements in the quality of neonatal care in the past decade would be reflected by a similar improvement in clinical outcomes in neonates born with very low birth weight.

Materials and methods

During a ten year study period from January 1, 2006 to December 31, 2015 we assessed outcome data from all 66 neonates born with less than 500 mg birth weight in the 1st Department of Gynecology and Obstetrics, Semmelweis University and subsequently treated at our Neonatal Intensive Care Center. We divided study subjects into two groups based on whether their birth date fell in the first half (2006–2010; n = 39) vs. the second half (2011–2015; n = 27) of the study period and compared clinical outcomes in the two groups. To investigate factors predicting mortality for neonates born with less than 500 g birth weight during the entire study period we assessed several clinical parameters comparing their relative frequencies among survivors versus mortality cases. For this purpose we divided cases representing the entire study period into a survival and mortality group.

A large number of clinical parameters were available for assessment as potential predictors for clinical outcome. These included maternal factors, obstetric data and neonatal factors.

Among *maternal factors* maternal age and parity, the number of prior gestations, previous assisted reproductive technique (ART) treatments and smoking during gestation were all assessed.

Among *obstetric factors* the presence of multiple pregnancy, gestational age at delivery, type and reason for preterm delivery, method of delivery, birth weight and neonatal gender were investigated.

Among *neonatal factors* prenatal steroid prophylaxis treatment, 1 and 5 min Apgar score, surfactant treatment, type and length of respiratory treatments, occurrence of neonatal complications like pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), postnatal echocardiography results, presence of persistent ductus arteriosus (PDA), type of treatment for PDA, intraventricular hemorrhage (IVH), periventricular leucomalacia (PVL), creation of a shunt for IVH, retinopathy of prematurity (ROP) with laser treatment, surgical intervention for necrotizing enterocolitis (NEC), pathological bone fractures developing during the neonatal intensive care stay, diaphyllin or caffeine treatments, the presence of congenital disease, cause of death, date and time of death were the main clinical parameters assessed.

Statistical analysis

We used different statistical methods on the basis of the nature of dependent variables and continuity of the independent variables. For instance, analysis of variance (ANOVA) was used if the dependent variables were dichotomous or nominal and the independent variables were continuous. In other cases cross table analysis was performed analyzing distribution of parameters after their conversion from continuous to categorical variables. Statistical difference was considered present if p value was below 0.05.

Results

Survival rate in the first half of the study period (2006–2010) was 30.8% with 27 total deaths (69.2%). 12 out of the total of 39 neonates with less than 500 g birth weight survived. In the second half (2011–2015) 19 out of 27 (70.4%) survived with a mortality rate of (29.6%; n = 8). The difference in survival rate between the two halves of the study period reached statistical significance ($p < 0.05$).

Comparing clinical parameters between mortality cases versus surviving infants for the whole study period (2006–2015), we found that among infants who died maternal age was not significantly higher (32.4 ± 5.56 years) than for survivors (31.1 ± 5.52 years; $p > 0.05$).

With respect to previous pregnancies, means were not statistically different between the groups ($G_{surviving} = 1.9$, $G_{mortality} = 1.97$; $p > 0.05$). Similarly, in terms of parity means ($P_{surviving} = 1.29$, $P_{mortality} = 1.40$; $p > 0.05$) were not statistically different.

There was no significant difference in the rate of use of assisted reproductive technology (ART) in the surviving versus mortality groups. Among the surviving, 3 out of 31cases (9.7%) had been conceived through ART while in the mortality group a significantly higher proportion of cases was conceived through ART (5 out of 35 = 14.3%; $p > 0.05$).

There was a significantly higher rate of multiple pregnancy in the mortality group compared to the survivor group. In the mortality group, 12 out of 35 cases (34.3%) while in the survival group only 3 out of 31 cases (9.7%; $p < 0.05$) represented multiple pregnancy. This means that a neonate with less than 500 g birth weight born from multiple pregnancy had a mortality rate of 80% compared to a 45% mortality rate for single pregnancy (Fig. 1).

There was no significant difference between the mortality and surviving cases with respect to smoking during gestation. In the

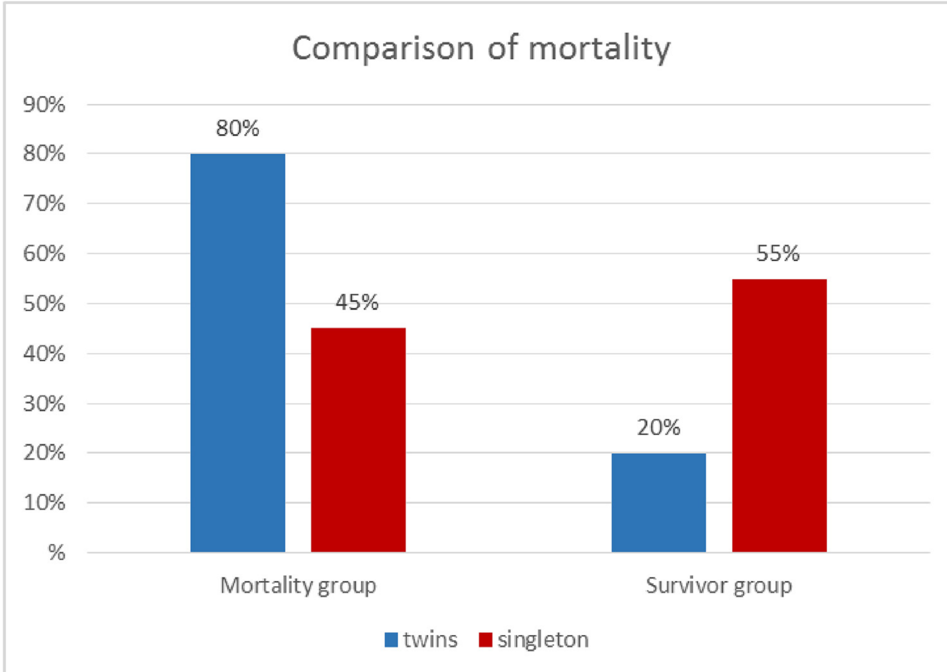

Fig. 1. Distribution of multiple pregnancy cases in the mortality versus survivor groups among premature infants with less than 500 g birth weight. The blue bars represent cases of multiple pregnancy, the red bars represent cases of single pregnancy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).
Nem kell a fenti cím, elég a magyarázó szöveg. Bal oldalon: mortality group, jobb oldalon survivor group. Az igen és nem nem kell, ez benne van a magyarázó szövegben.

mortality group 5 out of 35 (14.3%) while in the surviving group 4 out of 31 (12.9%; $p > 0.05$) had a history of smoking during gestation.

Gestational age at delivery was significantly higher for the survivor group (gestational $age_{surviving} = 25.35 \pm 1.4SD$ weeks) versus the mortality group (gestational $age_{mortality} = 24.07 \pm 1.9SD$ weeks; $p < 0.05$) (Fig. 2).

Table 1 shows the etiology for premature delivery. As described in the table, among the surviving cases premature delivery was associated almost in every case with either maternal hypertension (15 out of 31 = 48.4%) or intrauterine growth restriction (IUGR) (13 out of 31 = 41.9%). In contrast, in the mortality group premature rupture of the membranes and spontaneous premature labor were significantly more common. Premature rupture of the membranes occurred in 22.8% of the mortality versus 3.2% of the surviving groups ($p < 0.05$). Spontaneous preterm labor occurred in 22.8% of the mortality versus 6.4% of the surviving groups ($p < 0.05$).

There was a significant difference between the mortality versus survivor groups with respect to type of delivery. All surviving cases were delivered via cesarean section (31 out of 31 cases = 100%) whereas in the mortality group the proportion of babies delivered through cesarean section was only 28 out of 35 cases (80%; $p < 0.05$) the remaining 20% representing vaginal delivery.

Neonatal birth weight was not statistically different between the mortality versus the survivor groups. For the survivor group, group mean was 437.1 ± 52.5 g whereas for the mortality group it was 420 ± 61.5 g ($p > 0.05$).

Similarly, there was no statistically significant difference between the groups with respect to neonatal gender. Male to female ratio was 0.63 for the survival group while it was 0.45 for the mortality group ($p > 0.05$).

The frequency of prenatal steroid prophylaxis given to promote lung maturation was not statistically different between the groups. In the survivor group 24 out of 31 (77.4%) while in the mortality group 20 out of 35 (57.1%) received steroids for this purpose ($p > 0.05$).

Both 1 min and 5 min Apgar scores were significantly higher in the surviving compared to the mortality group. Mean 1 min Apgar score was $6.32 \pm 1.62SD$ in the survivor compared to $4.11 \pm 1.93SD$ in the mortality group ($p < 0.05$). Mean 5 min Apgar score was $8.10 \pm 1.32SD$ in the survival versus $5.86 \pm 2.31SD$ in the mortality group ($p < 0,05$) (Fig. 3).

A significantly higher number among the surviving subjects received surfactant (28 out of 31, 90.3%) compared to only 23 out of 35 (65.2%) in the mortality group ($p < 0.05$). Essentially, 12 out of 15 (80%) premature infants not receiving surfactant born with less than 500 g birth weight expired shortly after delivery (Fig. 4).

The dose of surfactant given was also significantly higher in the survivor group. Among infants who survived, mean dose of surfactant given was $163.8 \pm 64.5SD$ mg. In contrast, in the mortality group mean dose was only $93.5 \pm 76.6SD$ mg ($p < 0.05$).

Pulmonary hemorrhage did not occur among surviving subjects while it occurred in 6 out of 35 (17.1%) cases in the mortality group ($p < 0.05$).

Discussion

Perhaps the most noteworthy finding in our present study is that neonates born with less than 500 g birth weight between 2011 and 2015 had a more than two-fold improvement in survival compared to those born between 2006 and 2010 (70.4% vs. 30.8%). We believe that this trend reflects the results of our quality improvement efforts during the past decade at our institution in the area of gestational, obstetric and neonatal intensive care. This finding accords with previous data on a similar though smaller-scale improvement in survival reported by others [15]. In contrast, there is a recent study reporting on the lack of improvement in the survival rate of neonates with less than 500 g birth weight over a fifteen year period prior to 2012 [16].

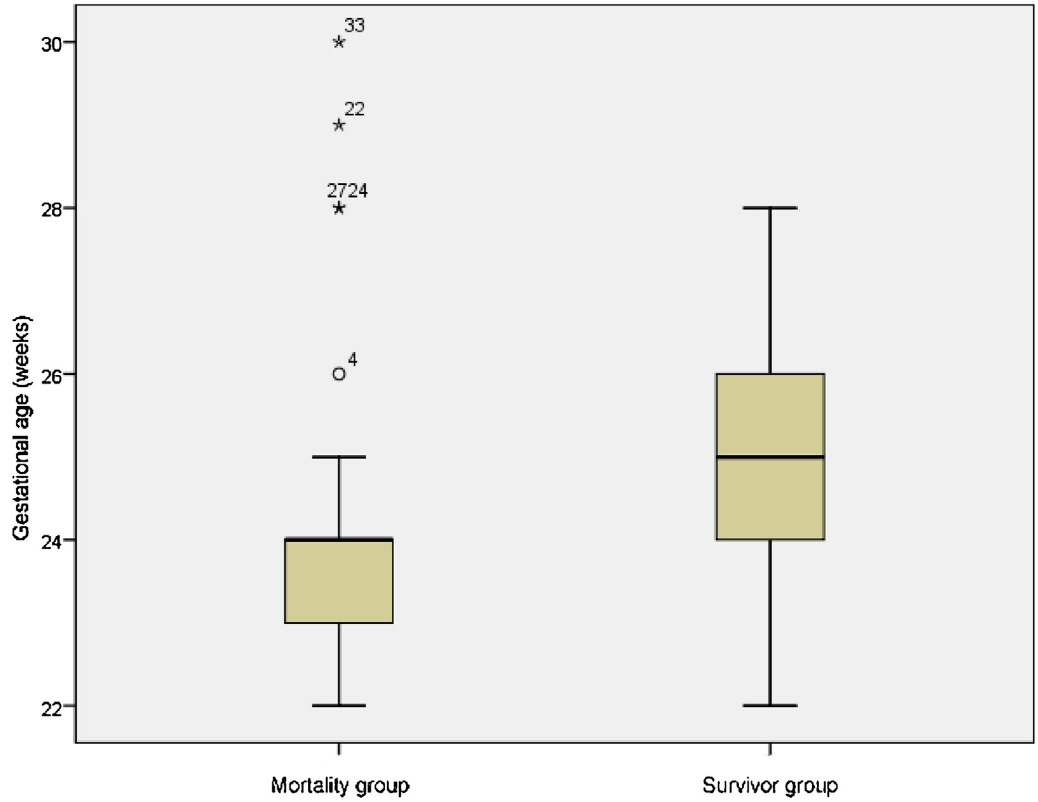

Fig. 2. Distribution of gestational age in the mortality versus survivor groups among premature infants with less than 500 g birth weight.
Y tengelyen: gestational age (weeks), bal oldalon alul: mortality group, jobb oldalon survivor group, nem tudom, hogy a számozott kicsi kör és csillagok mit jelentenek? A színes oszlopok és a függőleges vonalak standard deviation-t, ill. confidence interval-t jelentenek? Esetleg ezt érdemes részletezni?

It is particularly important to note that maternal age was not significantly different between the mortality and survivor groups, the means being almost numerically identical [17].

Another notable finding in our study, even if one considers the potential limitation in statistical evaluation due to the relatively low sample size, is the lack of significant association between the use of assisted reproduction techniques and mortality. It is well known that certain techniques such as ICSI may increase the risk for development of fetal chromosomal abnormalities. It is therefore all the more remarkable that assisted reproductive techniques did not seem to be associated with increased mortality of extremely small birth weight infants in our study population.

Multiple pregnancy is generally considered a high risk condition for obstetric complications. A relatively common adverse outcome after multiple pregnancy is premature delivery. Premature infants with less than 500 g birth weight born from multiple pregnancies did have a much higher mortality rate in our study population. It appeared that one of the key factors in this was the overall lower birth weight of premature infants from multiple pregnancies compared to those born from single pregnancies [17].

Table 1
Etiology of premature delivery among premature infants with less than 500 g birth weight. Numbers given represent the number of cases; percent distribution within the group is also shown.

Etiology of premature delivery	Survivors n = 31	Mortality cases n = 35
Abruptio placentae	0; 0%	3; 8.6%
Maternal hypertension	15; 48.4%	9; 25.7%
Premature rupture of the membranes	1; 3.2%	8; 22.8%
Intrauterine growth restriction	13; 41.9%	6; 17.1%
Spontaneous preterm labor	2; 6.4%	8; 22.8%
Induced preterm delivery	0; 0%	1; 2.8%

Though smoking shows no significant influence on the postnatal mortality in premature infants [18], may give a predisposition to IUGR; there is a well-established association between premature delivery and intrauterine growth restriction. This latter condition is in turn a recognized predictor for both postnatal morbidity and mortality [19,20].

The fact that among premature neonates with birth weight less than 500 g survivors had a significantly higher gestational age at delivery compared to the mortality group (25.35 ± 1.4 weeks versus 24.07 ± 1.9 weeks; $p < 0.05$) may imply that even as little as nine days may produce enough biological changes/maturation to result in significantly better survival chances. This conclusion may have important practical implications for everyday obstetric care drawing attention to the need to prolong gestational age even by a few days in case of threatening premature delivery

Among the survivors premature delivery was associated with maternal hypertension and/or intrauterine growth restriction in the vast majority amounting to no less than 90% of cases. In contrast, the distribution of conditions leading to premature delivery in the mortality group was much more even with maternal hypertension, intrauterine growth restriction, premature rupture of the membranes and spontaneous preterm labor sharing about equally. Taken together these conditions were responsible for nearly 90% of all cases.

In the background of both premature rupture of the membranes and spontaneous preterm labor, an infectious process is usually identifiable. Incidences for both conditions are usually low in premature delivery amounting to 3.2% and 6.4%, respectively. Our findings demonstrate that in cases where premature delivery is associated with an infectious process, survival is much lower compared to cases where premature delivery is primarily associated with maternal hypertension.

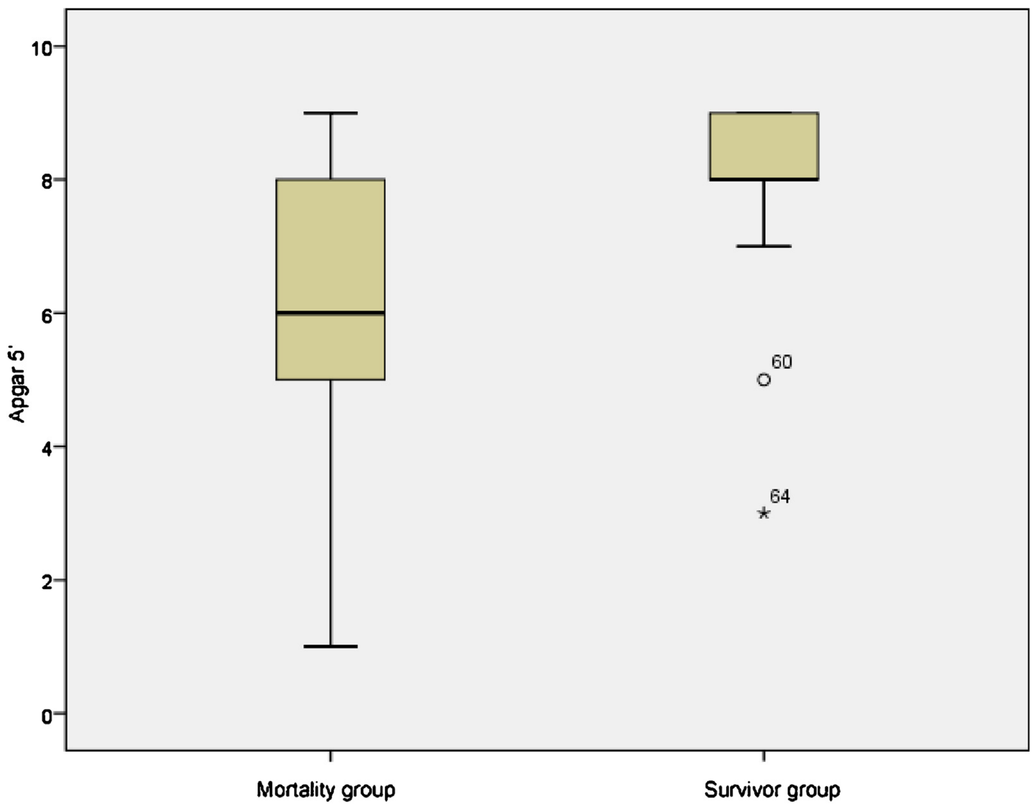

Fig. 3. Distribution of 1 min (above) and 5 min (below) Apgar scores in the mortality versus survivor groups among premature infants with less than 500 g birth weight. Balra mortality group, jobbra survivor group

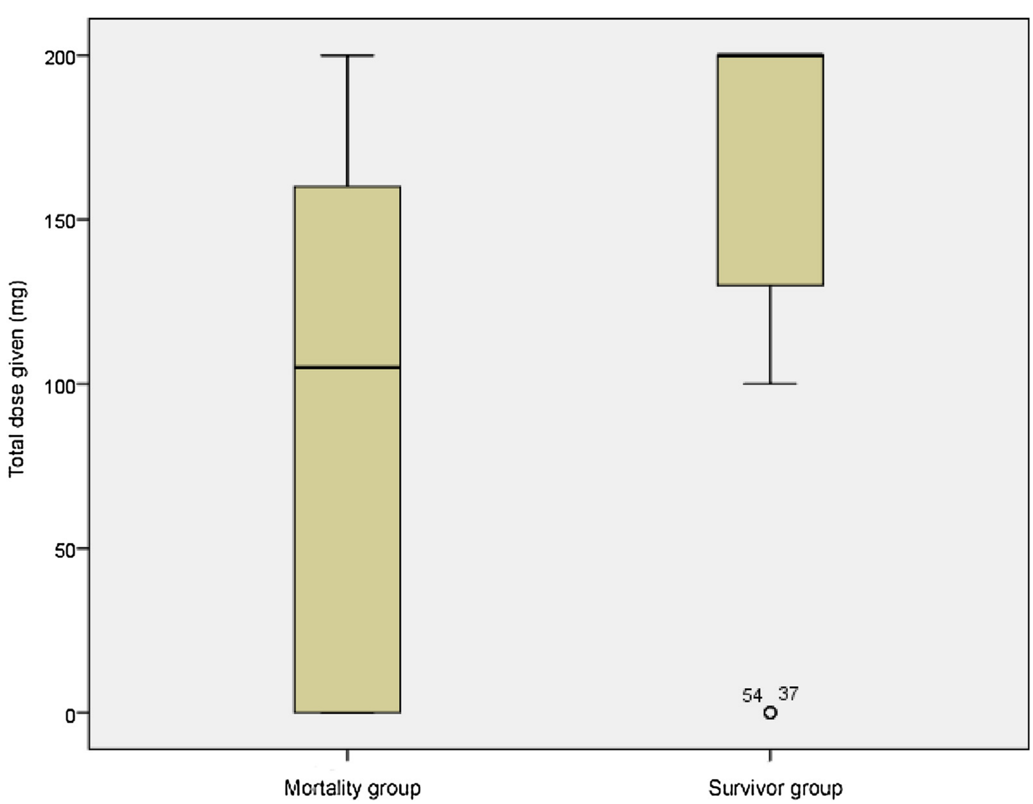

Fig. 4. Dose distribution of surfactant given for subjects in the mortality versus survivor groups among premature infants with less than 500 g birth weight. Balra mortality group, jobbra survivor group, Y tengelyen total dose given (mg)

We found that all surviving premature infants with less than 500 g birth weight were delivered by cesarean section as opposed to mortality cases where 20% were delivered by vaginal delivery. Previous reports did not find a similar difference between survivors and mortality cases in extremely low birth weight neonates. For instance, in a study by *Kyser* and coworkers the proportion of neonates delivered by cesarean section among survivors versus fatality cases was quite similar (68.8% for mortality cases and 64.6% for survivors) [21]. Other studies reported higher overall rates for cesarean section approximating 80% [16]. Some authors reported lower rates for cesarean section among premature neonates especially when expected birth weight was very low [22]. Such variability in policies regarding delivery methods in preterm delivery with extremely low birth weight point at the lack of consensus and the need for standard guidelines [23,24].

Our results do not support the belief shared by some authors regarding a lack of survival benefit for cesarean section among extremely low birth weight infants. Our data cannot be ignored by the treating clinicians especially when faced with threatened premature delivery due to an infectious process such as chorioamnionitis or intrauterine infection, conditions that markedly increase postnatal mortality [24].

Although we could not demonstrate a statistically significant difference between the survivor and the mortality groups in the rate of steroid prophylaxis given, a trend for a difference was seen (77.4% vs. 57.1% for the survivor and mortality groups, respectively) and it did appear that steroid prophylaxis was associated with increased postnatal survival. Previous reports unequivocally show this association between steroid prophylaxis and postnatal survival rates [25,26]. As previously mentioned, the prolongation of gestation in case of threatened premature delivery with extremely low neonatal birth weight by even a few days may be crucial in the attempts of improving postnatal survival. The time gained in order for the corticosteroid prophylaxis to take its full effect may be an important factor in this process.

Over 90% of the subjects in our study received surfactant treatment in order to improve postnatal respiratory function. Among premature infants with less than 500 g birth weight not receiving surfactant as many as 80% expired shortly after birth. We conclude that in the neonatal care of premature infants with extremely small birth weight appropriate dose of surfactant must be given to avoid severe complications and to improve survival.

In summary even with the limitation of a relatively low population size we were able to demonstrate a statistically significant improvement in postnatal survival for premature infants with less than 500 g birth weight treated at our institution during the study period. Detailed analysis of the data suggests that much of this improvement could be attributed to quality improvement in obstetric and neonatal intensive care undertaken at our institution during the study period. Additionally, our findings suggest that among premature infants with less than 500 g birth weight survival is worst when preterm delivery was associated with premature rupture of the membranes and/or intrauterine infection. This underlines the importance of preventing or promptly treating vaginal infections during gestation in an attempt to decrease the complications arising from intrauterine infection. These efforts could result in a markedly reduced postnatal mortality. Also a key point in this quality improvement the widespread use of prenatal steroid prophylaxis and a more intense continuous prenatal fetal screening.

Condensation

The 40% increase in the survival of premature infants with less than 500 g birth weight is due to the prevention and the treatment of vaginal infections during gestation, to the overall improvement in the quality of care of threatened premature delivery, regarding the widespread use of prenatal steroid prophylaxis, the more aggressive use of antibiotics, the tighter infection control and the more intense continuous prenatal fetal screening.

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