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STRATEGIES OF USING SURFACTANT: RESULTS OF THE FIRST POLISH NATIONAL SURVEY OF DAILY PRACTICE

STRATEGIE PODAWANIA SURFAKTANTU W CODZIENNEJ PRAKTYCE KLINICZNEJ. PIERWSZE POLSKIE BADANIE WIELOOŚRODKOWE

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Abstract

Background: The efficiency of routine practices in the management of neonatal respiratory distress syndrome (RDS) have never been systematically investigated in Poland.

Objective: To evaluate RDS treatment policies and short-term outcomes in neonatal intensive care units (NICUs).

Material and methods: We retrospectively analyzed medical records of premature neonates ≤ 32 weeks' gestation, diagnosed with RDS in level-2 and level-3 referral centers. Collected data: comprised clinical variables, antenatal corticosteroids, respiratory support, surfactant (SFT) policies and short term outcomes.

Results: Data of 987 infants from 53 NICUs were analyzed. The median gestational age was 29 weeks (range 22-32) and birth weight 1190 g (range 340-2860). Infants requiring SFT had significantly lower exposure to antenatal corticosteroids (75%) vs. those managed without SFT (83%, $p=0.006$). SFT was given to 59% infants in level-3 NICUs and 40% in level-2. There was significant variability of SFT use between level 2 and level 3 NICU. (9% to 100%). Poractant alfa was most commonly used (97%) in the median initial dose of 170 mg/kg (IQR 120-200). Single application was most frequent (79.8%). SFT administration methods were endotracheal instillation in babies maintained on mechanical ventilation (68.0%), INSURE (27.6%) and minimally-invasive delivery (MIST) 4.4%. Early rescue treatment remained core SFT strategy (57.4% cases), while prophylaxis accounted for only 13.3% cases.

Conclusions: There is considerable variation in the frequency of use of surfactant in Polish neonatal centers. Traditional intratracheal instillation with subsequent mechanical ventilation dominates, although newer methods INSURE and MIST are becoming increasingly popular. Early rescue SFT is a predominant strategy, which conforms to current standards. The rate of antenatal corticosteroids remains too low.

Key words: Respiratory Distress Syndrome, preterm infant, surfactant, daily clinical practice

Streszczenie

Efektywność rutynowych strategii leczenia zespołu zaburzeń oddychania (ZZO) u noworodków nie była jak dotąd w Polsce systematycznie analizowana.

Celem pracy była ocena sposobów i krótkotrwałych leczenia ZZO w oddziałach intensywnej terapii noworodka.

Materiał i metoda: Retrospektywnie analizowano dane noworodków o dojrzałości ≤ 32 tyg. ciąży z objawami zespołu zaburzeń oddychania leczone w oddziałach II i III stopnia referencyjności. Analiza dotyczyła: parametrów oceny klinicznej, prenatalnego stosowania sterydów, metod wspomagania oddechu, metod podawania surfaktantu oraz powikłań.

Wyniki: Oceniono dane 987 noworodków uzyskane z 53 oddziałów. Średni wiek ciążowy wyniósł 29 tygodni (zakres 23-32), a średnia masa ciała 1190 g (zakres 340-2860). Dzieci wymagające leczenia surfaktantem pochodziły z ciąż w których obserwowano znacznie niższy odsetek stosowania sterydów prenatalnych (75%) w porównaniu z dziećmi które nie wymagały podawania leku (83% $p=0,006$). W oddziałach III i II stopnia referencyjności surfaktant otrzymało odpowiednio 59% i 40% dzieci. Różnice w leczeniu surfaktantem były znaczące i wynosiły od 9% do 100%. Najczęściej stosowanym surfaktantem był Poractant alfa (97%) a stosowana średnia dawka wynosiła 170 mg/kg. Aż 79,8% dzieci wymagało tylko jednej dawki surfaktantu. Surfaktant podawany był najczęściej u dzieci wymagających leczenia sztuczną wentylacją (68%). Metodę INSURE zastosowano u 27,6% noworodków a MIST u 4,4%. Preferowana była wczesno-lecznicza podaż surfaktantu 57,4%. Profilaktycznie surfaktant zastosowano u 13,3% dzieci.

Wnioski: W polskich oddziałach neonatologicznych istnieje ogromne zróżnicowanie w stosowaniu surfaktantu. Surfaktant podawany jest głównie metodą tradycyjną z następową kontynuacją sztucznej wentylacji, chociaż nowsze metody aplikacji jak INSURE czy MIST znajdują coraz większe zastosowanie. Najczęściej stosowaną metodą jest wczesno-lecznicze podanie leku. Częstość prenatalnego stosowania sterydów jest zbyt niska.

Słowa kluczowe: zespół zaburzeń oddychania, wcześniak, surfactant, postępowanie kliniczne

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INTRODUCTION

In Poland, as in other European countries and the USA, the use of exogenous surfactant in the treatment of Respiratory Distress Syndrome (RDS) has become the gold standard since the end of the 1990s. However, the first European guidelines on surfactant use appeared no earlier than in 2007, and were later updated in 2010 [1]. Current recommendations on the use of surfactant in the care of premature infants with RDS were issued in 2013, based on the latest scientific data from studies published until 2012 [2, 3, 4]. The need for such frequent updates has its roots in numerous controversies on the most optimal methods of surfactant administration and dosing, as well as efforts to minimize treatment-related complications.

In various clinical situations, however, everyday clinical practices in Neonatal Intensive Care Units (NICUs) may fail to correspond with proposed therapeutic schemes. So far, we lacked reliable data on the use of surfactant in daily practice in Poland and our large-scale retrospective study is the first to address this need.

OBJECTIVES

The main goal of the project was to investigate the practices in the management of preterm infants with RDS. The results obtained will be used to develop strategies for implementation of a standardized approach to RDS therapy, including treatment with surfactant, based on the latest European guidelines.

MATERIAL AND METHODS

The retrospective analysis of clinical practices was carried out using conventional investigation tools: patient and center questionnaires.

With center questionnaires we obtained data on the number of premature neonates ≤ 32 gestational weeks (g.w.) with diagnosis of RDS including infants treated with surfactant from January 1, 2013 to June 30, 2013. Patient questionnaire encompassed the following data: gender, gestational age, birth weight, general condition in the first minutes of life as measured by Apgar score, history of antenatal corticosteroids, delivery room management, severity of RDS, type and length of respiratory support, method of surfactant administration and dosing regimen, incidence of BPD defined as oxygen dependency at 36 weeks of postconceptional age, and children's mortality.

We collected data from 53 hospitals in Poland, including 41 tertiary and 12 secondary referral centers.

Statistical analysis was exploratory in nature. With regard to categorical variables, absolute frequencies and percentages were calculated. Numerical variables were summarized descriptively – with means, medians, standard deviations, confidence intervals and ranges. For comparisons, the U-Mann Whitney test was used for continuous variables, and the Pearson chi-square test for categorical variables. A two-tailed level of significance (alpha value) was set at 0.05 for all analyses. Predictive factors of treatment modality were identified using logistic regression.

RESULTS

Patients

Out of the 987 analyzed infants, 52% were male and 48% were female, and the overwhelming majority of cases (91%) were inborn. Median gestational age was 29 weeks (range: 22-32 weeks) and median birth weight 1190 grams (range: 340-2860 grams). Thirty six percent were of extremely low birth weight (<1000 g).

Antenatal corticosteroids

In our cohort 749 (76%) infants received antenatal steroids. Of those, 576 (79.5%) received a single course and 149 (20.5%) two courses. Median treatment to delivery interval was 2 days (range 0.5h-60 days). Infants requiring surfactant had significantly lower exposure to antenatal corticosteroids (75%) vs. those managed without surfactant (83%, $p=0.006$)

Radiographic changes

RDS was radiologically confirmed in 755 (76%) neonates. On the basis of radiographic findings, grade I RDS was diagnosed in 22.4%, grade II – 37.6%, III – 31.5%, and grade IV in 8.5% of the babies. Children who required surfactant therapy presented with more extensive radiographic findings typical of RDS (median RDS grade 2 vs. 1; $p<0.0001$)

Surfactant treatment

A total of 710 children were treated with surfactant and these were subjects to detailed analysis.

Fifty percent of those neonates were at the gestational age of 26-30 weeks (median: 28 g.w.). Birth weight of half of the infants ranged between 800-1400 grams (median 1070 g). Infants with extremely low birth weight (<1000 g) accounted for 42% of the surfactant group.

The rate of surfactant use, assessed with center questionnaires was 57% for all NICUs, 59% (range: 12-100%) in tertiary and 40% (range: 9-63%) in secondary referral centers.

Most children (95%) received surfactant via the traditional route i.e. the endotracheal tube. Subsequent invasive mechanical ventilation was used in 483 infants (68.0%), whereas the INSURE (Intubation-SURfactant administration-Extubation) method was used in 196 neonates (27.6%). In this group 45 infants were extubated >1 hour from drug administration. The MIST method (surfactant delivered without tracheal intubation via a vascular catheter) was used only in 31 (4.4%) neonates (fig. 1).

Poractant alfa was the most common surfactant, administered in 97% cases. Median first dose was 170 mg/kg (IQR 120-200). Overall, 79.8%, 19.1%, and 1.1% of the newborns required one, two and three doses, respectively (fig. 2).

Fifty-seven percent of the children received early rescue treatment i.e. between 15 min and 2 h of life, whereas in 13.3% of the subjects surfactant was given immediately after birth in the delivery room. As many as 93% of extremely preterm infants without exposure to prenatal corticosteroids were treated with surfactant, but only 11% received the drug immediately after birth,

and 18% after hour 2 of life. In the rest -64% – surfactant was given between 15 min and 2 h of life (fig. 3).

Predictive factors for surfactant use

Analysis of predictive factors for surfactant use revealed a statistically significant effect of lower: neonatal maturity, birth weight, antenatal corticosteroid exposure, and Apgar score at 1 minute of life (fig. 4).

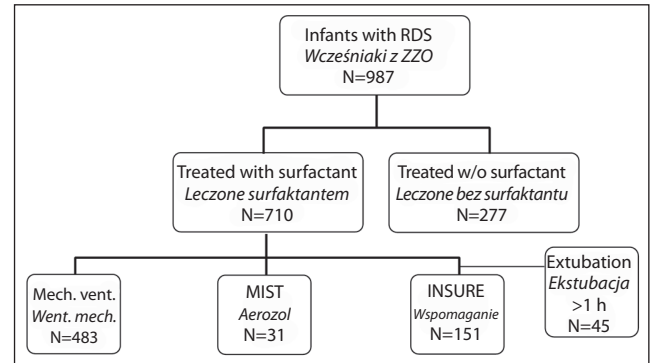


Fig. 1. Distribution of the study cohort in terms of treatment strategy.

Ryc. 1. Noworodki o dojrzałości ≤ 32 t.c. leczone i nieleczone surfaktantem oraz metody podawania surfaktantu.

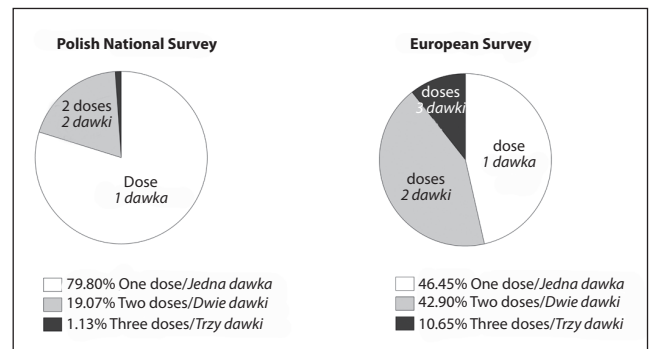


Fig. 2. Number of surfactant doses: comparison with the results of European survey [5].

Ryc. 2. Liczba dawek stosowanego surfaktantu (porównanie z danymi europejskimi [5]).

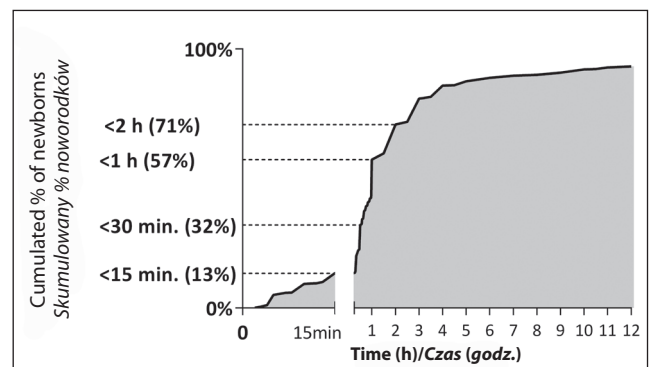


Fig. 3. Timing of the first dose of surfactant vs. birth.

Ryc. 3. Czas podania pierwszej dawki surfaktantu.

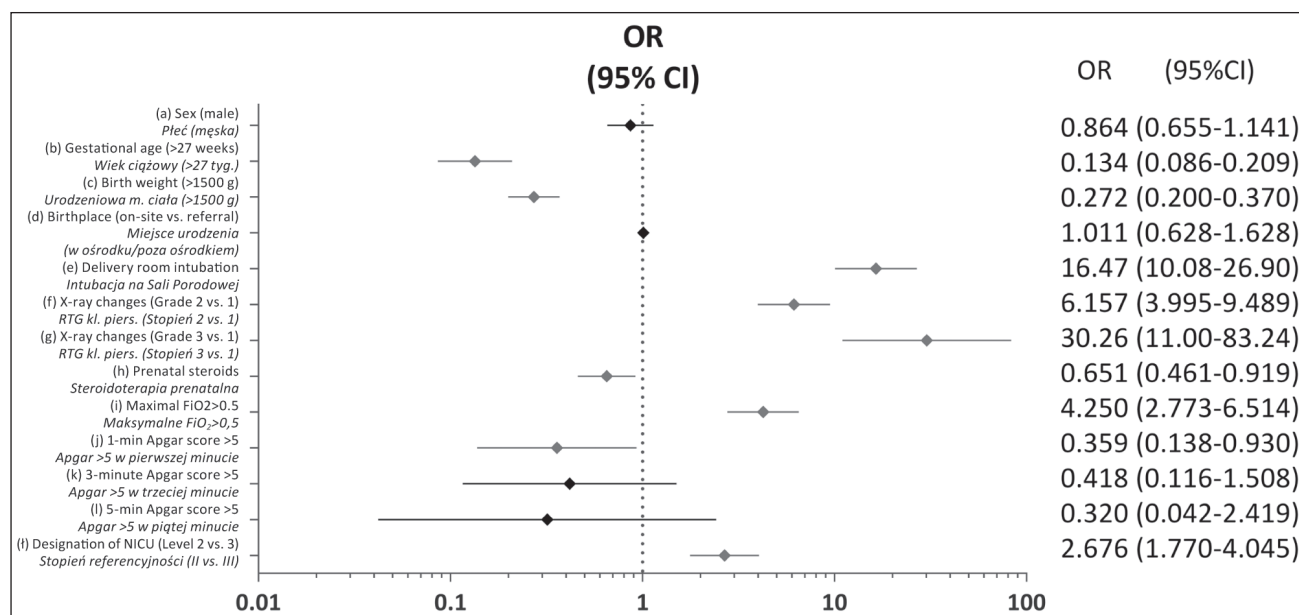


Fig. 4. Factors predictive of surfactant administration.

Ryc. 4. Analiza czynników predykcyjnych dla stosowania surfaktantu.

Bronchopulmonary dysplasia (BPD)

The rate of BPD defined as oxygen dependency at 36 weeks of postconceptional age, was 14.2% in the entire study group (N=987), and was lower (11%) in the 196 infants of the INSURE group.

Mortality

Out of 987 children 119 (12%) died. In the surfactant group, a statistically significantly lower rate of mortality was noted in the INSURE/MIST group as opposite to the mechanically ventilated infants (1.8% vs. 23.7%; $p < 0.0001$). After regression adjustment for baseline status, the use of invasive ventilation was still associated with increased odds for mortality (OR 7.16, 95% CI, 1.9-25.9).

DISCUSSION

In our study of 987 neonates (≤ 32 g.w.), median maturity in the group which received surfactant was 28 g.w. and was slightly higher than in the European study by van Kaam in 2011 [5].

Higher use of surfactant was observed in tertiary as compared to secondary referral centers (59% vs. 40%, respectively). Of note was the significant variability of surfactant use between centers (12-100% in tertiary and 9-63% in secondary referral NICUs) which indicateth lack of a uniform system of surfactant administration and poor compliance with European guidelines.

Although the previous European guidelines promoted prophylactic use of surfactant within 15 minutes of life, we found that early rescue surfactant strategy is predominant in the Polish neonatal units (57.4%) with median time to surfactant administration of 1 hour [1].

In our cohort, only 13% of the studied children received prophylactic surfactant treatment. Since the 2010, several important studies have been published that have re-evaluated the role of surfactant prophylaxis in the current era of early noninvasive respiratory support [5, 6, 7, 8, 9, 10].

The most recent European guidelines published in 2013 suggest treatment with surfactant as a standard, for extremely preterm infants, if the mother did not receive antenatal steroid therapy, and infants who require intubation for stabilization (before radiological confirmation of RDS) [2].

Endotracheal administration with subsequent mechanical ventilation was the dominant surfactant strategy and in our study was performed in 68% of the neonates. The INSURE (INTubation – SURfactant administration – Extubation) method first described by Verder et al, becoming increasingly popular in Polish neonatal units, was used in 27.6% in our study [11]. INSURE is especially useful in more mature newborns, who often may be extubated immediately after surfactant administration and continued on nCPAP/NIPPV. In accordance with the current European recommendations, clinical evaluation needs to be made in each individual baby, to assess possible tolerance of such management [2]. In our study 23% of the infants were extubated >1 hour after surfactant administration, which indicates insufficient knowledge of the INSURE method [12].

MIST (Minimally Invasive Surfactant Therapy), i.e. delivery of surfactant without tracheal intubation via a fine bore catheter, is the latest method, recommended especially by Italian and Australian neonatologists [13]. In our study, only 4.4% of infants requiring surfactant therapy received the drug using the MIST method.

In our infants poractant was the most commonly given surfactant (97% infants), at median first dose 170 mg/kg. majority (61%) were given the higher dose i.e. 150-200 mg/kg, contrary to the results of the European survey by van Kaam, where 100 mg dose was used in 58% of the babies [5].

The current 2013 European guidelines recommend repeated dosing in the evidence of ongoing RDS. such as persistent oxygen requirement and need for mechanical ventilation [2]. In our study, a single dose of surfactant turned out to be sufficient for nearly 80% of the children.

Out of the 710 neonates treated with surfactant, only 19.1% received more than one dose, whereas as little as 1.1% required three doses (fig. 2). Thus, we did not analyze the criteria for the administration of the second and third dose, but we intend to perform it in our future prospective trial. Also Ramanathan in his study conducted in 20 U.S. centers in 293 newborns with birth weight between 750-1750 g, demonstrated a notably lower need for the second dose of surfactant if 200 mg of Curosurf were given [14]. Significantly different data have been demonstrated by van Kaam study, where as many as 42.9% of newborns required the second and 10.6% - the third dose of surfactant (fig. 2). This indicates better efficacy and a definite advantage of using the higher 200 mg/kg dose as compared to 100 mg/kg [5, 14].

A total of 118 infants died in the studied group, which accounts for 12% of the whole cohort. Mortality rates among babies treated with a less invasive methods (INSURE and MIST) vs. those treated with mechanical ventilation were statistically significantly different and were 1.8% and 23.7%, respectively. Nevertheless, it is vital to bear in mind that neonates who received surfactant using INSURE or MIST were more mature and had a lower level of baseline severity.

The choice of traditional way of administering surfactant, with subsequent mechanical ventilation, was influenced by the extent of the radiologic changes in the lungs ($p=0.0016$), but also strongly mediated by the allocation of a patient to a given medical center ($p=0.0000008$). This shows that besides objective factors like radiography findings, treatment modality is driven by hospital habits.

Our study complements the European survey by van Kaam, conducted in 173 European NICUs, yet *having half the sample size of our study, among which there were no Polish centers* [5].

CONCLUSIONS

1. Significant differences were noted regarding the rates of surfactant use in newborns at ≤ 32 g.w. in Polish neonatal centers (9-100%).
2. Tracheal administration – followed by artificial ventilation – is the dominant method of surfactant administration, although the popularity of the INSURE and the MIST methods is being observed.
3. Early treatment and prevention are the most (57%) and the least (13%) common treatment strategies in the Polish second and tertiary neonatal units, respectively.

4. A total of 80% of the newborns who received 200 mg/kg Curosurf do not require subsequent doses of surfactant.
5. The rate of antenatal corticosteroids (76%) in Polish secondary and tertiary referral centers remains too low.

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