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USING THE AUTOMATED FIO_2- SPO_2CONTROL IN NEONATAL INTENSIVE CARE UNITS IN POLAND. A PRELIMINARY REPORT

ZASTOSOWANIE AUTOMATYCZNEJ KONTROLI FIO_2- SPO_2 W ODDZIAŁACH INTENSYWNEJ TERAPII NOWORODKA W POLSCE. DONIESIENIE WSTĘPNE

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Abstract

Aim: *Analysis of the way in which a new method of implementing the automated control of oxygen therapy during respiratory support is applied in newborns with respiratory failure.*

Material, methods and results: *The AVEA-CLiO$_2$ ventilator with automated FiO_2- SpO_2 control was used in our study of 121 newborns conducted between February 2014 and January 2015 in five neonatal intensive care units.*

A web-based database was used to gather information entered concurrently with using the FiO_2- SpO_2 control system. This included demographics, clinical status, clinical indications, as well as objective and subjective experience.

Among the 121 newborns 94 were preterm and 27 were near-term (33-36 hbd). The primary indication for using the system was "routine management" of FiO_2 during respiratory support and it was generally initiated within the first 2 days of life. Many of the newborns were managed with the system for more than a week. The control range was usually 90%-95% SpO_2, though sometimes it was lower or wider. The control range was not related to the newborn's maturity or indication for use. The perception of more "frequent and persistent" SpO_2 alarms was lower when the alarms were set loosely. There were no reports of the system not working effectively.

Conclusions: *We expect this first report of the routine use of automated FiO_2- SpO_2 control to be useful not only to other centers in Poland but also to all those adopting this important new technology. Our registry continues and we expect to have an update when we have experience with 1000 infants. Carefully controlled trials are also needed to refine the optimum use of automated FiO_2- SpO_2 control and to quantify its impact on neonatal outcomes.*

Key words: neonate, intensive care, respiratory support, oxygen control

Streszczenie

Cel: *Ocena nowej metody automatycznej kontroli tlenoterapii podczas stosowanego wsparcia oddechowego u noworodków z niewydolnością oddychania.*

Materiał, metody i wyniki: *Do badań 121 noworodków zastosowano respirator AVEA-CLiO_2 z automatyczną kontrolą tlenoterapii. Badanie przeprowadzono w okresie: luty 2014-styczeń 2015 w 5 ośrodkach intensywnej terapii noworodka.*

Do elektronicznej bazy danych wprowadzano na bieżąco wyniki zastosowania metody automatycznej kontroli FiO_2- SpO_2. Stanowiły je dane demograficzne i kliniczne, wskazania kliniczne, obiektywne wyniki leczenia jak i subiektywna opinia badacza. Pacjentami były głównie noworodki przedwcześnie urodzone (94), a jedną piątą stanowiły tak zwane „późne wcześniaki" (27), czyli noworodki urodzone blisko terminu porodu (33-36 hbd). Podstawowym wskazaniem do zastosowania metody było "rutynowe postępowanie" z FiO_2 podczas stosowanego wsparcia oddechowego, zazwyczaj włączane w ciągu pierwszych 2 dni życia. U wielu noworodków system ten stosowano powyżej jednego tygodnia życia. Stosowano zakres saturacji 90-95%, aczkolwiek niekiedy nieco wyższy lub niższy. Zakres ten nie zależał od dojrzałości dziecka ani od wskazań do leczenia. Postrzeganie alarmów SpO_2 jako „częste i uporczywe" było mniejsze, jeśli granice alarmowe nastawiono szerzej.

Wnioski: Sądzimy, że pierwsze doniesienie o rutynowym stosowaniu metody automatycznej kontroli FiO_2- SpO_2 będzie przydatne nie tylko dla ośrodków w Polsce, ale także innych ośrodków wdrażających tę nową ważną technologię.

Nasz rejestr jest kontynuowany, zamierzamy uaktualnić wyniki po zgromadzeniu danych 1000 noworodków.

Konieczne są także dalsze, starannie zaplanowane badania kliniczne, aby dokładnie określić optymalne zastosowanie metody automatycznej kontroli FiO_2- SpO_2 i ocenić jej wpływ na wyniki leczenia noworodków.

Słowa kluczowe: noworodek, opieka intensywna, wsparcie oddechowe, kontrola tlenoterapii

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INTRODUCTION

It is generally accepted that the management of oxygen therapy has a marked impact on the outcomes of extremely premature infants. This applies specifically with regard to SpO_2 targeting. Recent reports demonstrate that the shifting of SpO_2 target ranges has a highly relevant effect on long-term outcomes of extremely preterm infants, not only in the evaluations of changes in clinical practice but also in large, randomized, controlled trials [1-4]. Large, well-controlled multicenter trials intended to identify the best target range have also reminded us of the important balance between the risks of excess and inadequate oxygen [4, 5]. Some have speculated that the nurse's ability to minimize time outside the target range is more important than the exact target range [5-8]. Indeed, the challenges of manually titrating FiO_2 to manage SpO_2 exposure in routine care are well accepted and documented [9-12].

Interest in automating the adjustment of FiO_2 in neonatal ventilation is not new, with the first of many publications having come out in 1979 [13]. With improved technology and a better understanding of the potential clinical impact, systems intended for clinical use are becoming available. These systems offer the promise of significant labor savings and a more effective control of oxygenation. The first of such automated control systems became available in Europe in 2012. The effectiveness of this system has been clinically validated [14-18]. It has been in routine use in a group of tertiary care Polish Neonatal Intensive Care Units (NICUs) since 2012.

The Polish Neonatal Society often collects information about the use and outcomes associated with the adoption of new technology [19-21]. Accordingly, a national registry of the use of the FiO_2- SpO_2 control system was developed.

AIM

Analysing the implementation of a new method of automated control of oxygen therapy during respiratory support applied in newborns with respiratory failure.

MATERIAL, METHODS AND RESULTS

Under the direction of the Polish Neonatal Research Board, a web-based database was developed at the Medical University of Silesia. No individual patient data are reported and there is no investigational intervention. Therefore, the Ethics Committee of the Medical Centre of Postgraduate Education in Warsaw determined that consent of neither the Ethics Committee nor the parents was needed.

The automated FiO_2- SpO_2 control system used in Poland is the AVEA-CLiO_2, (Yorba Linda California USA). The system can be used during invasive and noninvasive

ventilation, and the automated FiO_2- SpO_2 function is an option that can likewise be activated if desired. The AVEA system has been widely used for the care of neonates for over a decade. However, the automated FiO_2- SpO_2 control option ($CLiO_2$) is newer and was introduced in Europe in 2012. It uses a rule-based algorithm that continuously monitors the oxygen saturation via an integrated pulse oximeter (Radical, Masimo Corp., Irvine, California). The algorithm makes a decision about whether the FiO_2 should be adjusted every second. The rules vary depending on whether SpO_2 is above, below or within the set target range. The response is much faster when SpO_2 is below the target range. In addition, the size of the adjustment is based on the magnitude, duration, trajectory of the SpO_2 excursion and also the previous FiO_2 that had maintained SpO_2 within the target range during stable periods. The Great Orchestra of Christmas Charity donated 11 ventilators with automated FiO_2- SpO_2 control to the 5 centers that participated in the study.

The database includes 53 descriptive fields that are gathered during the course of treatment and entered by the site coordinator. Entries are reviewed by the data center and clarified as deemed necessary. These cover demographics, the delivery room status of the infant, the course of treatment in the NICU, specific information about the use of the system, and discharge outcomes. Demographic parameters include administration of prenatal steroids, the method of delivery, estimated gestational age (EGA), and birth weight. Clinical parameters include delivery room resuscitation (maximum FiO_2 and method), use of surfactant, respiratory support before and after automated intervention (duration, method, minimum and maximum FiO_2). Parameters during automated interventions include: indications for use, FiO_2 levels (before, min/max during and final), initial and subsequent SpO_2 target range, alarm settings (tight – 1% above or below the SpO_2 target or loose – more than 1% above or below the SpO_2 target), and subjective assessment of the effectiveness of the automated system (very well, well, moderate, poor) and alarm frequency (frequent and persistent, frequent not persistent, infrequent or rare).

The indications for use and rating characterizations are a forced choice from a list. Discharge and 28-day outcome parameters include survival, severe Retinopathy of Prematurity (ROP), Bronchopulmonary Dysplasia (BPD), and Intraventricular Haemorrhage (IVH). ROP was determine das severe if it requiredlaser therapy. BPD was classified asthe need for oxygen therapy and/or respiratory supportat 28 days of life. The progression of the disease was defined as light if at 36 weeks PMA the patient did not require oxygen; as average if FiO_2 was 21-30% for at least12 hours per day, and severe if FiO_2>30%,or there was necessary respiratory support. IVH was determined by the Papile scale (I-IV).

Five centers participated in the registry from its inception in February 2014. The NICUs in the centers are of similar size (6-12 beds). The number of admissions that required respiratory support varied between 130-251 per year. The centers differed in the percentage of outborn newborns (52%, 19%, 10%, 10% and 0%). All centers had significant practical experience with the ventilator and automated system before the start of the registry, each having used it routinely for at least one year.

There were some differences in the standard of practice in the use of the new system among the centers. This ventilator system was the newest type at all the centers and used as their primary ventilator for intubated newborns. However, its use for non-invasive support varied. All five centers used another system for elective noninvasive support. One center used it only for intubated infants. Three continued its use when the newborn was transitioned to noninvasive support. Finally, all but one intervened with the system and automated FiO_2- SpO_2 control, if a noninvasively ventilated infant was unstable.

Statistical evaluations were made using chi-square for categorical data and for continuous data either Mann--Whitney or t-tests depending on the distribution of the data. These analyses were conducted using SigmaXL (version 6.1 Toronto Canada). P values <0.05 were considered statistically significant.

During the one-year evaluation period (February 2014-January 2015), 121 infants were managed with the automated FiO_2- SpO_2 control system at the 5 centers. Enrollment varied between centers, consistently with the numbers requiring respiratory support and the standard of practice described above. The demographics and maximum oxygen in the delivery room of the 121 infants is detailed in table I. It is tabulated according to maturity (preterm (<33 weeks EGA and near-term infants). Most of the infants were preterm with a median birth weight of 900 grams (IQR 640-1085). The birth weight of the near-term group was 2610 grams (IQR 2130-2800). The maximum FiO_2 required in the delivery room was higher in the preterm group (P=0.002) (tab. I).

The clinical course in the NICU prior to initiation of automated FiO_2 control and the indications for its use are summarized in table II. It is tabulated under the preterm/near-term categories. Maximum oxygen requirements in the NICU prior to initiating automated FiO_2 control reflect deterioration from the delivery room requirements. They were similar between the two groups with a trend for a higher requirement in the near-term infants. Automated FiO_2 control was initiated on the first day of life in more than half the infants and within the first 3 days of life in 65%. Nevertheless, intervention much later in the clinical course was common, occurring from 13-50 days in 20% of the infants. The difference in the indications for use in the two maturity groups was statistically significant (P<0.001). Nevertheless, the most common indication for use in both groups was for routine control, rather than to address a specific clinical problem. The most common other indications for use were for frequent desaturation episodes in the near-term infants (22%) and frequent desaturation episodes or weaning from oxygen in preterm infants (6%). Use of the system was initiated during noninvasive ventilation in 18% of the infants. These infants were older (0.07 vs 4.3 days, P=0.0190) on lower levels of oxygen (0.24 vs 0.40 P<=0.001), but of similar weight and gestational age. As noted above, this group would be infants with frequent desaturations on standard noninvasive support.

When the automated FiO_2- SpO_2 system was initiated, the $FiO_2$was 0.30 (IQR 28-50). The median duration of

Table I. Demografic and clinical characteristics of neonates prior to initiation of Auto FiO_2- SpO_2.
Tabela I. Charakterystyka demograficzna i kliniczna noworodków przed włączeniem Auto FiO_2- SpO_2.

	Preterm ***Przedwcześnieurodzone***	**Near Term** ***Urodzone blisko terminu porodu***	**p**
Number *Liczebność*	94	27	-
EGA (weeks) *Wiek płodowy (tygodnie)*	26 (24-28)	34 (34-36)	<0.001
Birthweigh (grams) *Urodzeniowa masa ciała [g]*	900 (640-1085)	2610 (2130-2800)	<0.001
Max FiO_2 in delivery room *Max FiO_2 na sali porodowej*	30 (30-50)	25 (21-40)	=0.002

Data shown as count, percent or median (IQR)
Preterm defined as EGA <33 weeks, Near Term 33-36 EGA.
Dane wykazane jako liczba, odsetek lub mediana. Przedwcześnie urodzone definiowane jako wiek płodowy poniżej 33 tygodni ciąży, urodzone blisko terminu porodu: 33-36 tygodni ciąży.

Table II. Clinical characteristics of neonates prior to initiation of Auto FiO_2- SpO_2.
Tabela II. Charakterystyka demograficzna i kliniczna noworodków przed włączeniem Auto FiO_2- SpO_2.

	Preterm ***Przedwcześnie urodzone***	**Near Term** ***Urodzone blisko terminu porodu***	**p**
Number *Liczebność*	94	27	-
Min FiO_2 in NICU *Min. FiO_2 w OITN*	28 (21-30)	24 (21-40)	ns
Max FiO_2 in NICU *Max FiO_2 w OITN*	50 (40-92)	90 (45-100)	=0.077
Age Auto FiO_2- SpO_2 (hours) *Wiek w chwili włączenia FiO_2- SpO_2 [h życia]*	19 (1-320)	26 (5-64)	ns
RoutineUse (%) *Wskazanie: użycie rutynowe*	94%	70%	<0.001

treatment with the automated FiO_2- SpO_2 system was 3 days (IQR 1.4-8.1), which was followed by a median of 13.8 days (IRQ 5.2-28.1) of respiratory support.Of the 121 cases, 17 did not survive to 28 days. Table III describes the course of automated treatment, categorized by survival. Of the survivors, nearly 50% were placed on the system in the first day of life. During a median automated treatment of 3 days, their FiO_2 was weaned substantially, that is from a median of 0.35 to 0.24, with more than a quarter on room air. A few infants did not survive to 28 days. These infants started automated FiO_2- SpO_2 much earlier in life but with a comparable initial FiO_2. They were treated for a slightly longer period of time but during this period there was a marked deterioration and doubling of FiO_2 (tab. III).

The most common SpO_2 target range settings were 95%-90% (71%), and a lower range in 22% (87% or 88%). The span between the high and low control levels was typically 5 (73%), rarely tighter and 6-8 in 25%. In all but 2 cases, the midpoint of the target range was between 90% and 93%. These differences in the SpO_2 target range were center-specific rather than patient-specific. There were no differences in control range settings associated with EGA or with indication for use. Target range settings were unchanged over the course of treatment in 93% of the infants. When changed, it was more often tightened.

The alarms were set tightly, that is to trigger when just exceeding the control range, 50% of the time. The span between the high and low alarms, in the cases when they were not set at the control range, was much wider

Table III. Summary of Auto FiO_2- SpO_2 Treatment: Decedents & Survivors (28d or discharge).
Tabela III. Porównanie przebiegu leczenia z auto FiO_2- SpO_2 w grupie zgonów i przeżyć (28. doba życia lub wypis).

	Survivors ***Przeżycia***	**Decedents** ***Zgony***	**p**
Number *Liczba*	104	17	-
Preterm (% <33 weeks EGA) *Przedwcześnie urodzone (% <33 tyg. ciąży)*	75%	94%	ns
Age at Auto FiO_2- SpO_2 (hours) *Wiek w chwili włączenia auto FiO_2- SpO_2 (h)*	29 (4-267)	3 (0-18)	=0.002
FiO_2 at Auto FiO_2- SpO_2 start (%) *FiO_2 przy włączaniu auto FiO_2*	35 (25-50)	40 (33-75)	ns
FiO_2 at end (%) *FiO_2 w dniu końcowym*	24 (21-35)	98 (55-100)	<0.001
Duration of Auto FiO_2- SpO_2 (days) *Długość stosowania auto FiO_2- SpO_2 (d)*	3 (1-8)	6 (2-9)	ns
Duration of support after Auto (days) *Długość kontynuacji wsparcia oddechowego po auto FiO_2- SpO_2 [d]*	14 (6-30)	5 (0.4-9)	=0.018

Data shown as count, percent or median (IQR)
Dane wykazane jako liczba, odsetek lub mediana.

Table IV. Perception of Auto FiO_2- SpO_2 performance.
Tabela IV. Postrzeganie przydatności Auto FiO_2- SpO_2.

	Very Good ***Bardzo dobre***	**Good** ***Dobre***	**Moderate** ***Średnie***	**Poor** ***Złe***	**P**
All *Wszystkie*	44%	54%	2%	0%	-
Routine use-other use *Zastosowanie rutynowe* *- zastosowania pozostałe*	47% 21%	52% 72%	1% 7%	0% 0%	=0.063
Preterm - Near term *Urodzone przedwcześnie -* *urodzone blisko terminu porodu*	47% 33%	51% 67%	2% 0%	0% 0%	ns
Survived - Died *Przeżycia - zgony*	39% 71%	59% 29%	2% 0%	0% 0%	=0.054

(10 IQR: 7-13). High alarm, when not set at the high control limit, was typically set 3 higher than the top of the control range. When not set at the low control limit, it was most often set at 85% SpO_2. These differences in the SpO_2 target range were center-specific.

The subjective assessment of the automatic FiO_2 function was rated as "Very Good" or "Good", in 98% of the cases. There was a trend in the ratings associated with the indication for use and survival, but not infant maturity, as shown in table IV. The systems' performance was more likely to be rated as having worked "VeryWell" for the "routine use" indication and in those subjects who died. The users also reported on their assessment of the frequency of SpO_2 alarms. They were mostly rated as either "Frequent and Persistent" (59%) or "Frequent" (22%). The balance was rated as "Infrequent" or "Rare". There was a marked difference in the perception associated with whether the alarms were set tightly or loosely (P<0.001). The most noticeable difference was in the rating of "Frequent and Persistent" with 6% as compared to 37% when the alarms were set tightly (tab. V).

Table V. Alarm perception by tightness of alarm.

Tabela V. Postrzeganie alarmów w aspekcie ustawienia granicalarmowych.

	Tight Alarm settings *Wąskie granice alarmowe*	**Loose Alarm settings** *Szerokie granice alarmowe*	**p**
Number *Liczba*	59	62	-
Frequent and persistent *Częste i uporczywe*	39%	6%	<0.001
Frequent not persistent *Częste i nieuporczywe*	37%	79%	<0.001
Infrequentorrare *Nieczęste lub rzadkie*	23%	15%	<0.001

Tight a Alarm settings – 1% above or below the SpO_2
Wąskie granice alarmowe – 1% powyżej lub poniżej zakresu SpO_2
Loose a Alarm settings – more than 1% above or below the SpO_2
Szerokie granice alarmowe – >1% powyżej lub poniżej zakresu SpO_2

DISCUSSION

There are numerous published evaluations of the performance of this automated FiO_2- SpO_2 system [14-18] and more than 2 000 are in clinical use. We believe however, that this report of the patterns of its use is the first report of how the FiO_2- SpO_2 system is actually being used clinically. We found that the system was used primarily for routine management of infants who were intubated, often for periods of weeks. There were no reports of the system not working properly, in fact the perception of the system's functioning was quite positive. Some of our findings relating to our routine practices warrant discussion.

The SpO_2 control range was mostly set according to the European Guidelines of 90-95% [22], but sometimes lower. There is some support for the latter [5]. The control range was seldom changed during the course of treatment. The selection of the control range did not differ according to infant maturity or age, but rather among centers.

Some reports have led to speculation that the best practice might evolve towards a different SpO_2 targeting range in different clinical situations [3, 5, 23, 24]. While still needing evaluation, several examples of proposed targeting strategies are worth consideration. It might be appropriate to use higher target ranges for near-term infants. It might also be reasonable to change the target range based on post-conception or post-natal age. Furthermore, regardless of age, the labile respiratory status of some infants makes them more susceptible to marked desaturations. These infants might benefit from a higher target range. In practice such changes would necessitate managing different target ranges for different infants in the NICU and be very difficult to implement with manual FiO_2 control. However, they might well be practical to implement with an automated control system, just as ventilator settings are set according to each infant's needs.

In studies of manual control, lower target ranges have resulted in an increase in both mortality and important neonatal morbidities [4]. These troubling outcomes are believed to be associated with increased exposure to hypoxemia, which might be reasonably reduced by using a higher target range. One study showed that a lower target range was harder to maintain without automated control [17]. However, the consequence of a higher target, both during manual and automated control, was an increase in hyperoxemia. In the same study, automated control during use of a lower target range resulted in reduced exposure to hypoxemia as compared to manual control. This suggests that clinically effective use of lower target ranges might be practical with automated control systems.

We found that looser settings of the SpO_2 alarms resulted in a perception of a reduction in excessive alarms. This is not necessarily better, as persistent alarms might well be appropriate for some unstable infants. However, we speculate that moving from frequent and persistent to frequent alarms is probably good, as it reduces the risk of alarm fatigue that could lead to alarms being ignored. Many episodes of desaturation are a result of transient disordered breathing and spontaneously resolve. If these episodes trigger an alarm it is perceived as a false alarm, as no intervention was necessary. The threshold levels and delay for the alarms needs to carefully considered. The use of tight alarms, set to trigger when the target range is exceeded, comes from a perspective that an SpO_2 alarm that persists should be an indication that the baby needs assessment, and perhaps a change in FiO_2. The inadequacy of this intervention in resolving the oxygenation problem should result in another alarm that ought to be met with increased priority. In contrast, during automated control, the FiO_2 is continually being adjusted to keep the SpO_2 in the set target range. An SpO_2 alarm that persists during automated control is an indication that adjustments made to the FiO_2 have not mitigated the situation. It is our clinical impression, supported by studies of the automated control system [14-17], that manual adjustments to FiO_2 are only needed a few times per day. We feel this supports consideration of a different

paradigm in selecting the alarm thresholds and delays for use during automated control. We suggest that this consideration might well lead to setting alarms much wider than the set control range, with delays longer than typical practice. Optimal levels need to be evaluated.

All the evaluations of the automated FiO_2- SpO_2 control have been physiological crossover studies. Looking at differences within subjects necessitates crossover periods of 1 day or less. One study did evaluate crossover every 12 hours over 3 days [15]. We found that the system is used for management over longer periods. It is reassuring that the clinical perception of effectiveness over these longer periods was positive.

This is a relatively small observational study. Most of the data are objective, however the perceptions of system performance are completely subjective and prone to inter-observer variation. The results should be evaluated accordingly. Still, it seems reasonable to assume this approach would detect incidences of aberrant system performance. Experience with 121 subjects over 12 months at 5 centers is a reasonable first report, but also limited. With the small number in the subgroup comparison, clinically relevant differences might not have been detected. This is an ongoing project and we expect the experience from more centers in Poland, reflecting many more cases, will not only be more robust and diverse but also permit evaluation of trends in our practice.

CONCLUSIONS

We expect this first report on the routine use of automated FiO_2- SpO_2 control experience will be useful to all the centers adopting or refining its use. It will certainly start a dialog of optimal target ranges and alarm settings in Poland, and hopefully elsewhere. Our registry continues and we plan to have an update when we have experience with 1,000 infants. This system clearly saves labor by eliminating the need for manual titration of FiO_2, and has been shown to be effective in controlling oxygenation. However, controlled trials are needed to refine the optimal use of automated FiO_2- SpO_2 control and quantify its impact on neonatal outcomes.

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