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Incidence of Intermittent Hypoxemia Increases during Clinical Care and Parental Touch in Extremely Preterm Infants

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Keywords

Apnea of prematurity · Hypoxia · Oxygen desaturation · Skin to skin · Respiratory function

Abstract

Objectives: An increased frequency of intermittent hypoxemia (IH) is associated with a higher risk for poor developmental outcomes, disability, or death in extremely preterm infants. The objective of the prFesent study is to quantify the effect of hands-on medical and parental interventions on the incidence of IH in extremely preterm infants. ***Methods:*** An observational design with intraindividual comparisons was used. Blood oxygen saturation levels (SpO_2) and time-lapse video were recorded. Frequency, duration, and time to occurrence of IH (SpO_2 <80% for ≥10 s) were compared between nursing and medical care (NMC), health care by parents, skin-to-skin contact (SSC), touch in incubator, physiotherapy, and rest. Each infant was observed for six consecutive 24-h periods. Inclusion criteria were as follows: gestational age ≤28 weeks, birth weight <1500 g, postnatal age 0–6 weeks, gavage feeding, no severe illnesses or invasive procedures, no mechanical ventilation. ***Results:*** The highest proportion of time with IH occurred during NMC (2.49%) and incubator touch (1.32%), the lowest during SSC (0.74%) and health care by parents (0.67%). IH frequency per hour was highest during NMC (2.95, IQR 1.19–4.01) and lowest during SSC (0.88, IQR 0.37–2.32, $p < 0.001$). While an increase in IH during NMC was expected, the high incidence during incubator touch was surprising. Parental touch in the incubator is intended to be soothing, not stressful. ***Conclusions:*** Future studies need to clarify how preterm infants process touch, which attributes of touch are fundamental trigger mechanisms of IH, and which handling strategies are most effective in lowering the incidence of IH during hands-on medical care.

Introduction

Almost all extremely preterm infants (gestational age <28 weeks) and infants with very low birth weight (<1,500 g) experience intermittent hypoxemia (IH) during the first few months after birth [1, 2]. IH is considered a consequence of immature respiratory control and, therefore, is directly associated with prematurity apnea [2]. Research attempts have recently been made to disentangle

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the relationship between neonatal hypoxemia and later neurodevelopmental impairments or mortality [1, 3]. So far, it is difficult to distinguish whether hypoxemia is the cause or the consequence of brain abnormalities associated with neurodevelopmental disabilities [4]. Analyses have shown that infants who experience more desaturation events (SpO_2 <80% for ≥10 s) are at higher risk for disability or death than infants with low incidence [1]. In line with this, an increased frequency of IH is associated with a range of poor outcomes, including language and cognitive delays, impaired growth, motor impairment, cardiovascular impairment, retinopathy of prematurity, impaired control of breathing, bronchial asthma, bronchopulmonary dysplasia, and intraventricular hemorrhage [5–8]. It has been discussed that repeated hypoxemia/reoxygenation may cause sequelae by initiating a pathological oxidative stress-induced cascade [2, 9]. According to this, episodic hypoxemia and subsequent reoxygenation have the potential to sustain proinflammatory processes that can result in multisystem morbidity [2]. Various studies have shown that both long (>1 min) and short (20 s–1 min) desaturation episodes are associated with poor outcomes [1, 10, 11]. Especially, the combination of lower oxygen saturation levels (SpO_2 85–89%) and a high incidence of IH may increase the risk of death in small for gestational age and extremely preterm infants [11].

Therapeutic approaches to prevent IH comprise careful oxygen supplementation, respiratory support, and methylxanthine therapy [2, 6, 12]. Results of several studies indicate that various interventions could reduce the occurrence of IH: for instance, it has been observed that fewer desaturations occur during skin-to-skin contact (SSC; kangaroo care) than during prone or supine position in the incubator [13] or swaddled holding (supine in parents' arms, dressed/wrapped) [14]. Two other studies found increased desaturations during SSC, which might be explained by positional factors interfering with respiration (e.g., infant neck flexion) [15, 16]. On the other hand, it is well known that both environmental stress and medical handling can increase IH frequency [17]. Long et al. [17] showed that both frequency and quality of handling influenced the occurrence of hypoxemia in moderately preterm infants (mean gestational age 33 weeks). Levy et al. [18] suggested that in term and late preterm neonates (gestational age at birth >35 weeks) at risk for cerebral dysfunction due to severity of illness or seizures, handling for the provision of medical care was more likely to result in oxygen desaturation than handling for technical adjustments.

To date, no study has quantified the impact different caregiving interventions have on the incidence of IH in extremely preterm infants during routine neonatal intensive care. We investigated whether there are differences in the frequency, duration, and time to occurrence of IH during various kinds of caregiving. The primary goal of this study was to determine in how far medical care and other handling procedures might have detrimental effects on the incidence of IH.

Methods

Study Design

An observational design with intraindividual comparisons was used. This study followed the STROBE reporting guidelines and was registered under DRKS00018085.

Participants

Preterm infants were recruited at a tertiary care neonatal department during the data collection period from September 25, 2019, to November 1, 2020. Neonates had to meet the following inclusion criteria: gestational age ≤28 weeks, birth weight <1,500 g, gavage feeding, postnatal age 0–6 weeks, and parental written declaration of consent. Exclusion criteria were as follows: severe illness (e.g., sepsis) or congenital malformation of the infant, neonates requiring surgery or invasive mechanical ventilation. The study protocol was approved by the University of Leipzig ethics review board, reference number: 265/18-ek. Parents and personnel were informed that the infant would be monitored by a time-lapse camera and that vital parameters would be used to analyze IH; however, they were blind to the specific research question.

Measurements

Neonates were monitored with a time-lapse camera (TLC200Pro; Brinno Inc., Taipei City, Taiwan) at a sampling rate of one frame per second. Per infant, 6 days of consecutive 24-h periods were recorded. Oxygen saturation data and heart rate were continuously sampled with a pulse oximeter; the averaging time was set to 2 s (Masimo, Radical-7, Yorba, CA, USA). Segments with missing values (e.g., during pulse oximeter change, low perfusion, or poor signal quality) were excluded before averaging and IH detection. Less than 1.6% of measurement values were excluded. IH episodes were defined as oxygen saturation <80% for ≥10 s.

Two independent raters viewed the time-lapse videos and identified six distinct kinds of interventions (different modes of human interaction) which the neonates encountered: nursing or medical care (NMC), handling or nursing care by parents (NMCparents), SSC/kangaroo care, incubator touch by parents, physiotherapy, and rest (for a detailed description of interventions, see online suppl. Materials; see www.karger.com/doi/10.1159/000527725 for all online suppl material). The interventions were mutually exclusive and had to last a minimum of 5 s to register as a distinct episode. The entire recording time of each participant was subdivided into these interventions exact to the second. To do so, we developed a software that combined and synchronized the time-lapse data and the vital parameters. Markers were set (by hand) at the beginning and end of each intervention. IH were marked automatically by the

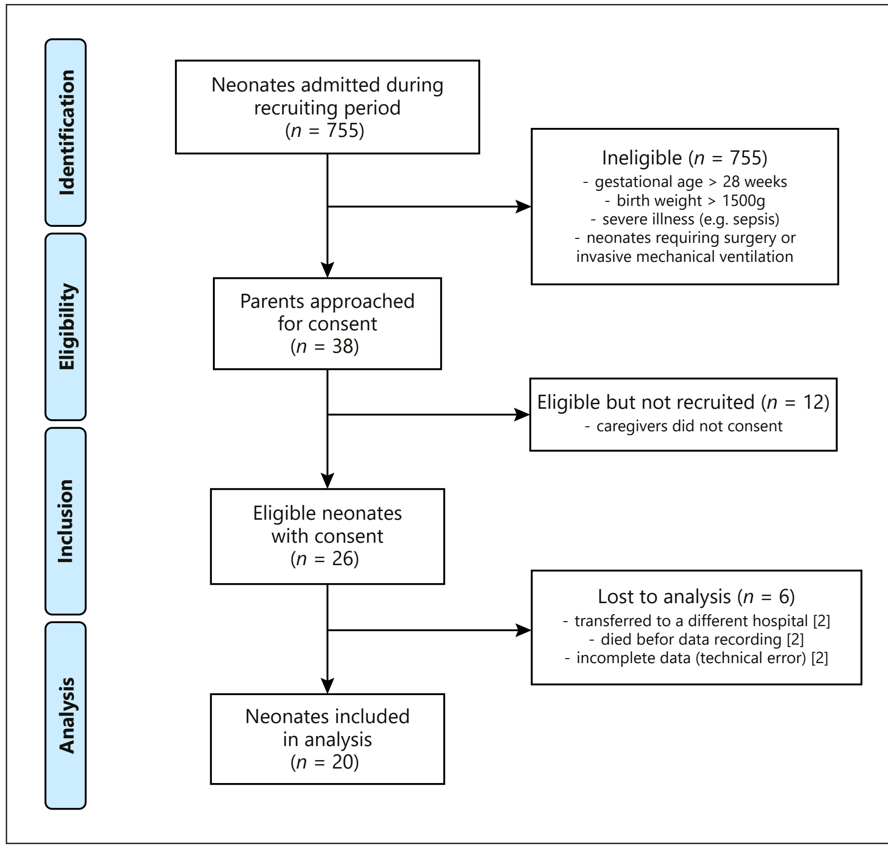

Fig. 1. STROBE flowchart.

aforementioned software. The software extracted the frequency, duration, and vital parameters of each intervention and IH episode.

The start of an IH defined to which intervention it was counted. IH episodes that required treatment but began during other interventions were not marked as NMC to prevent distortion of the SpO_2 values of NMC. Therefore, the frequency of IH during NMC represents only those IH that began during NMC. Similarly, the frequency of IH during all other interventions represents only those IH that began during the respective intervention. All data were aggregated per infant.

Statistical Analyses

Comparisons between interventions were conducted by nonparametric repeated-measures analysis of variance (Friedman tests). Post hoc pairwise comparisons (Wilcoxon signed-rank tests) and corresponding effect sizes are reported in online suppl. Tables S1 and S2. Alpha level was set at 5%. Data analyses were performed using SPSS 27 (IBM Corp.).

Results

Twenty neonates (ten female) participated in the present study (Fig. 1). Table 1 summarizes the patient demographics. All neonates received respiratory support (continuous positive airway pressure [n = 12] or noninvasive positive pressure ventilation [n = 8]), methylxanthine therapy (oral caffeine citrate [5–7 mg/kg/day], M = 6.22, standard deviation = 1.35), and were gavage fed. Two infants had a subependymal bleed. None of the participants had an intraventricular hemorrhage ≥2°. Within the 6 days of measurement, they received a median of 8.62 h (interquartile range [*IQR*] 6.50–12.53, min = 4.92 h, max = 20.51 h) of SSC. Pulse oximeter oxygen saturation (SpO_2) alarm targets were set at 87–94% and monitored continuously.

Valid oximetry and time-lapse recordings were available for a median of 5.96 days (*IQR* 5.72–6.03). Across this measurement period, the median percentage time of hypoxemia was 1% (*IQR* 0.63–2.29), with the least affected infant reaching only 0.12% of the recorded time with hypoxemia. In comparison, the most affected infant reached 5.75%, equating to a total of 8 h 23 min with oxygen saturation below 80% in 6 days. Bradycardia occurred during median 0.68% (min = 0.03, max = 3.22) of hypoxemia episodes.

The median IH episode length was 24 s (*IQR* 16–43; max = 446). Median SpO_2 during IH episodes was 76%

Table 1. Clinical characteristics of study participants

Mothers at infants' birth	*Mdn*	*IQR*	Min–max
Mother's age in years	33	29–38	21–39
		Frequency	Percent
Ethnicity white Caucasian		20	100%
Antenatal corticosteroids		20	100%
Birth mode			
Spontaneous		2	10%
Primary cesarean		6	30%
Secondary cesarean		12	60%
Singleton pregnancy		14	70%
Infants at birth	Mdn	IQR	Min–max
Gestational age, weeks	25	25–26	23–28
Birth weight, g	845	675–923	445–1,090
Body length at birth, cm	34	32–34	27–38
Apgar 5 min	8	7–8	5–9
Apgar 10 min	8	7–9	6–9
Infants during study period	Mdn	IQR	Min–max
Weight/start of study, g	1,060	904–1,183	530–1,370
Age/start of study, days	22	18–28	11–37
IH <60 s (frequency/day)	25	17–43	3.33–72.17
IH >60 s (frequency/day)	3	2–10	0.17–26.50

Mdn, median; IQR, interquartile range; IH, intermittent hypoxemia.

(*IQR* 73–78; min = 46). Median frequency of occurrence per day was 24.67 (*IQR* 16.42–43.38) for IH <60 s and 3.17 (*IQR* 1.58–10.21) for IH >60 s.

The six interventions constituted different percentages of the total recording time. Rest was the most prevalent (78.9%), followed by NMC (8.1%) and skin to skin (6.7%). Time during which the neonate was touched or caressed by parents while in the incubator made up 2.5%, health care performed by the parents constituted 1.9%, and physiotherapy amounted to 0.8%. One participant did not receive physiotherapy. The six interventions differed significantly in mean duration ($\chi^2 = 89.32$, $p < 0.001$), SpO_2 ($\chi^2 = 58.94$, $p < 0.001$; Fig. 2a), and heart rate ($\chi^2 = 46.17$, $p < 0.001$) (for distribution data, see Table 2).

Hypothesis 1: Proportion of Time with Hypoxemia Differs between Interventions

We found highly significant differences in the proportion of time with IH ($\chi^2 = 28.57$, $p < 0.001$; Fig. 2b): the highest percentage share of IH was associated with NMC (2.5%), followed by incubator touch (1.3%) and physiotherapy (0.9%). Percentage shares of IH during rest, SSC, and NMCparents were 0.85, 0.74, and 0.67%, respectively (distribution data are reported in Table 3c).

The difference in proportion is not due to IH duration as median duration of IH did not differ between interventions ($\chi^2 = 7.76$, $p = 0.170$; Table 3a). The drop in SpO_2 during IH episodes seemed to be more severe during NMC and incubator touch ($\chi^2 = 11.85$, $p = 0.037$; Table 3b); however, Bonferroni-corrected post hoc pairwise comparisons did not reach significance (online suppl. Table S1).

Hypothesis 2: Frequency of Desaturation Differs between Interventions

In sum, the most IH episodes were registered during rest (69.8% of all IH) and NMC (16.4%). Due to the different durations of the interventions, the times were standardized to make the incidence comparable (IH per hour).

Significantly, more IH per hour occurred during NMC (*Mdn* 2.95) than during NMCparents, SSC, physio, and

Table 2. Descriptive statistics: duration of interventions and median SpO_2 and HR during interventions

Intervention	*N*	Length of interventions, s				During intervention					
						SpO_2			HR, bpm		
		M	SD	min	max	Mdn	IQR		Mdn	IQR	
							25	75		25	75
NMC	20	381.01	64.57	263.74	511.93	90.02	87.79	90.81	169.47	163.41	176.02
IH_inter[a]	20	70.77	42.98	17.58	211.46	83.02	80.19	85.51	153.84	147.09	167.43
NMCparents	19	929.51	610.38	199.25	3,239.00	90.42	87.99	92.50	167.97	163.41	175.48
Skin to skin	20	7,565.22	2,072.09	4,431.78	11,473.00	91.38	89.46	92.60	162.04	156.42	167.30
Incubator	20	392.11	271.17	76.50	1,009.24	90.83	89.27	92.03	165.21	158.60	169.56
Physio	19	1,068.39	178.64	687.00	1,313.50	90.09	89.03	91.80	168.45	163.78	176.86
Rest	20	2,275.54	534.59	1,265.48	3,390.13	91.17	89.19	92.17	164.05	159.47	171.97

NMC, nursing or medical care; SpO_2, blood oxygen saturation levels; HR, heart rate; Mdn, median; IQR, interquartile range; M, mean; SD, standard deviation; s, seconds; bpm, beats per minute. [a] IH_intervention: hands-on treatments of acute hypoxemia were excluded from NMC to prevent distortion of SpO_2 and HR.

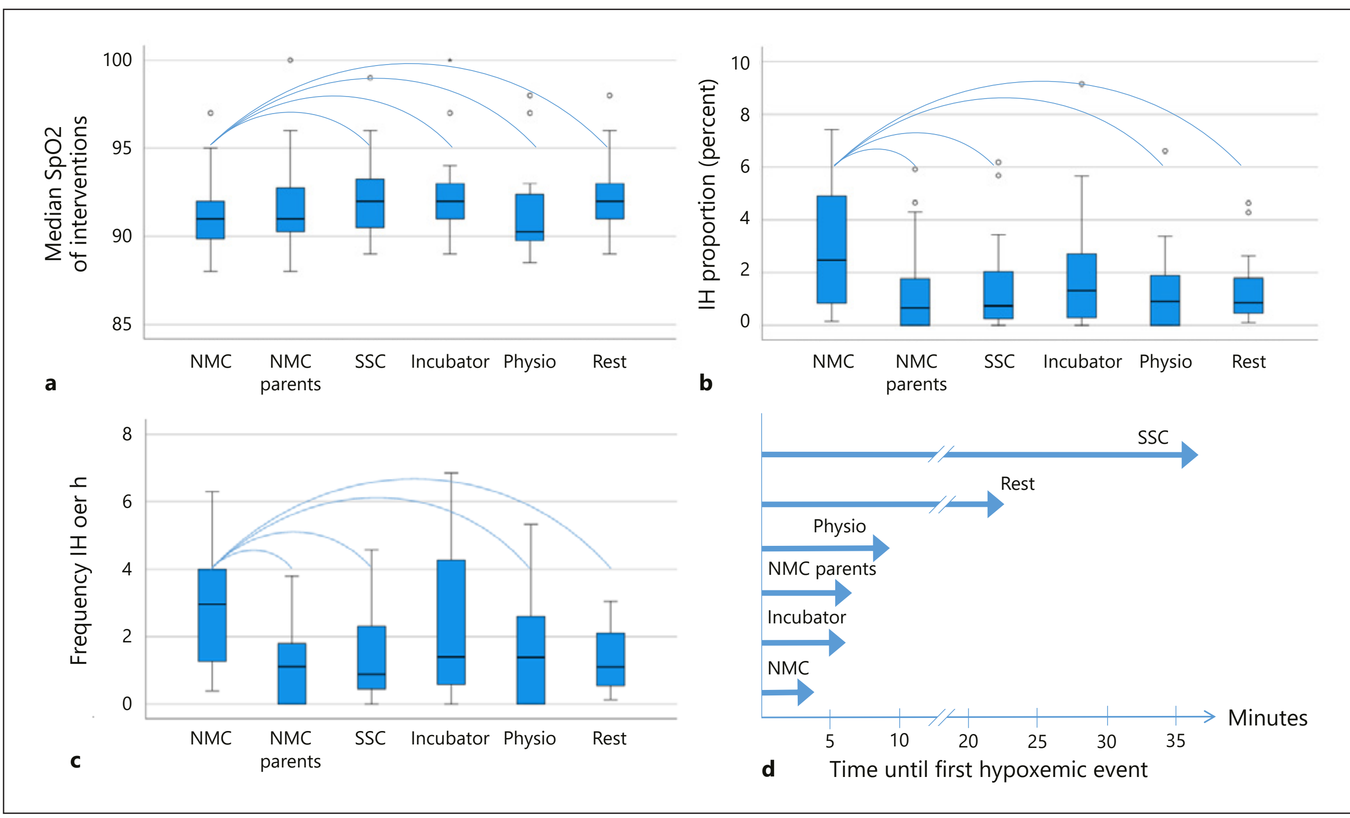

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Fig. 2. a–d Incidence of hypoxemia during different interventions. Arches indicate significant differences. Pairwise comparisons and effect sizes are reported in online suppl. Tables S1 and S2. Circles and stars indicate outlier values. **a** Median SpO_2 per intervention. **b** Proportion (time) of hypoxemia per intervention. **c** Frequency of oxygen desaturation per intervention. **d** Time elapsed until first hypoxemic event depending on intervention. For distribution data, see Table 3e. NMC, nursing or medical care; IH, intermittent hypoxemia; SSC, skin-to-skin care.

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Table 3. Descriptive statistics of hypoxemic episodes per intervention

a Length of hypoxemia episodes in seconds

	N[a]	M	(SD)	Mdn	(IQR 25–75)[b]
NMC	20	33.42	(11.57)	35.28	(24.34–42.35)
NMCparents	14	32.49	(18.02)	27.40	(19.00–42.82)
Skin to skin	19	30.38	(12.53)	26.00	(19.33–43.82)
Incubator	17	31.86	(12.95)	31.50	(21.75–43.00)
Physio	13	28.53	(16.66)	22.80	(15.17–44.17)
Rest	20	32.03	(9.60)	30.36	(25.41–37.84)

b Average SpO2 (in %) during hypoxemic episodes

	N[a]	M	(SD)	Mdn	(IQR 25–75)
NMC	20	74.46	(5.13)	76	(73–78)
NMCparents	14	76.20	(3.75)	77	(75–78)
Skin to skin	19	75.92	(4.36)	77	(74–78)
Incubator	17	73.74	(5.55)	75	(72–77)
Physio	13	75.19	(3.09)	76	(73–78)
Rest	20	75.04	(4.57)	76	(73–78)

c Proportion of hypoxemia in %

	N[c]	M	(SD)	Mdn	(IQR 25–75)
NMC	20	2.99	(2.31)	2.49	(0.75–4.94)
NMCparents	20	1.37	(1.78)	0.67	(0.00–1.97)
Skin to skin	20	1.48	(1.79)	0.74	(0.21–2.12)
Incubator	20	2.06	(2.39)	1.32	(0.29–3.03)
Physio	20	1.34	(1.68)	0.91	(0.00–1.89)
Rest	20	1.29	(1.29)	0.85	(0.43–1.79)

d Frequency of hypoxemia per hour

	N[c]	M	(SD)	Mdn	(IQR 25–75)
NMC	20	2.82	(1.72)	2.95	(1.19–4.01)
NMCparents	20	1.29	(1.28)	1.10	(0.00–1.84)
Skin to skin	20	1.43	(1.32)	0.88	(0.37–2.32)
Incubator	20	2.34	(2.25)	1.40	(0.58–4.49)
Physio	20	1.73	(1.79)	1.38	(0.00–2.78)
Rest	20	1.29	(0.93)	1.09	(0.53–2.18)

e Elapsed time until the first hypoxemic episode in seconds

	N[d]	M	(SD)	Mdn	(IQR 25–75)
NMC	11	274.68	(128.13)	216.00	(168.27–380.75)
NMCparents	11	516.24	(631.22)	323.00	(183.80–520.43)
Skin to skin	11	2,193.61	(1,066.53)	2,260.33	(1,096.50–2,995.00)
Incubator	11	413.59	(353.65)	309.75	(87.00–842.89)
Physio	11	502.71	(292.47)	463.00	(238.33–731.33)
Rest	11	1,413.18	(433.87)	1,296.51	(1,138.29–1,612.97)

M, mean; SD, standard deviation; Mdn, median; IQR, interquartile range; NMC, nursing or medical care. Post hoc pairwise comparisons are reported in online suppl. Tables S1 and S2. [a] Number of infants who experienced hypoxemic events during each intervention. [b] Desaturation events of less than 10 s duration were excluded. [c] During some interventions, only a subset of infants experienced hypoxemic episodes (see[a]); in these cases, proportion and frequency of hypoxemia were zero. [d] Intraindividual comparison of those 11 infants who experienced hypoxemic episodes during all six interventions.

rest ($\chi^2 = 26.79$, $p < 0.001$). Touch in the incubator (*Mdn* 1.40) was not statistically significant from NMC (Fig. 2c). SSC showed the lowest incidence (*Mdn* 0.88; Table 3d).

The highest frequency per hour of IH with durations longer than 60 s was also observed during NMC. IH >60 s occurred in 14 infants during NMC, in 18 infants during rest, in 8 infants during SSC, and in 0, 1, and 4 infants during NMCparents, incubator touch, and physio, respectively. Intraindividual comparisons were conducted of those eight infants who experienced long IH during rest, NMC, as well as SSC. The results indicated a significantly higher frequency of long IH during NMC (*Mdn* 0.79, *IQR* 0.39–1.13) than during SSC (*Mdn* 0.29, *IQR* 0.14–0.76) or rest (*Mdn* 0.35, *IQR* 0.13–0.76; $\chi^2 = 7.00$, $p = 0.03$).

Hypothesis 3: Elapsed Time until First Hypoxemic Episode Differs between Interventions

Within-subject comparisons showed highly significant differences in the time that passed until the first desaturation occurred depending on the situation the neonate encountered ($\chi^2 = 36.506$, $p < 0.001$; Fig. 2d; Table 3e). The shortest time elapsed during NMC and incubator touch (1–5 min). On the other hand, during SSC, a median of 37 min passed until oxygen desaturations occurred.

Discussion

The present study investigated the impact of handling situations on IH in extremely preterm infants. The six interventions we observed differed significantly in median SpO_2. This was most likely due to the difference in frequency of IH. In our study, NMC was associated with the significantly highest rates of short and long IH and the highest proportion of time with IH of all interventions. The lowest incidence was during SSC, NMCparents, and rest. The other interventions (incubator touch and physio) ranged in between. We found that less time elapsed to occurrence of desaturations during NMC, incubator touch and physio than during SSC and rest. Time to occurrence of IH was shortest during NMC (*Mdn* 3 min) and longest during SSC (*Mdn* 37 min). Levy et al. [18] have reported in their observational study of severely ill near-term infants that desaturations occurred within 60 s in 19.5% of all contacts inside the isolette. Handling for provision of clinical care was more likely to result in oxygen desaturation than handling for technical adjustments or other contacts [18]. Based on these and our findings, we infer that intensity, pain-, and stressfulness of handling may be relevant factors for IH. This is in line with other reports that found fewer apneic events [19] and fewer desaturations [13, 20] during SSC than during prone or supine position in the incubator or during swaddled holding [14]. In contrast, two studies by Bohnhorst et al. [15] showed an increase of IH during SSC with currently unknown cause [16]. Improvements in infant positioning during SSC in the last two decades might have reversed the influence of SSC on IH.

Premature infants are exposed to a multitude of potentially stressful interventions and painful stimuli during their stay in the NICU [21]. Repeated neonatal pain-related stress has been associated with poorer cognitive, motor, and behavioral development in children born extremely preterm [22]. It is evident that different procedures differ in their stress- and painfulness and that intrusive medical procedures are more stressful than routine care like diaper change [23]. In the present study, health care performed by parents had a significantly lower incidence of IH than clinical care performed by medical staff. This may at least partially be due to more painful procedures performed by medical staff. However, different (more gentle) handling strategies used by parents (e.g., during diaper change) may also play a part. Some findings hint at the possibility of reducing IH during stressful procedures by applying more gentle nursing and medical care [17, 21, 24]. In experimental analyses, diaper change has been used as a standard nursing procedure to compare different handling approaches: results indicate that diaper change in the incubator may be more stressful than during skin to skin [21]. The authors found a greater increase in skin conductance and decreased SpO_2 during incubator diaper change [21]. A different study showed that developmental care during diaper change (consisting of offering motor support by hand swaddling, non-nutritive sucking, and materials for grasping) significantly decreased pain scores and hypoxemic events [24].

Furthermore, supportive static contact and SSC have been shown to reduce stress and pain expression in extremely preterm infants during medical interventions [21, 24]. Long et al. [17] reported that the quality of handling changed when medical personnel used the SpO_2 readings as an indicator of infant stress. By modifying their handling or ceasing completely until the infant's oxygenation recovered, nurses actively reduced and shortened the amount of desaturations. Even though it is currently unknown how much minimizing IH would improve the neurological outcome, the present study helps quantify the association between medical care procedures and their inherent risk of causing IH. Furthermore, it is interesting to note that parental NMC was associated with lower IH rates (n.s.) than parental touch in the incubator. This is surprising because incubator touch is intended to be soothing, not stressful. More research is needed to understand how preterm infants process stroking and other forms of touch and which characteristics of touch are unpleasant for preterm infants.

In our study, handling during NMC was not standardized and differed depending on the personal style of medical personnel [25]. Future studies should use experimental settings to investigate which handling strategies are most effective in lowering the incidence of IH, e.g., by applying the recommendations of NIDCAP (Newborn Individualized Developmental Care and Assessment Program). It is unlikely that IH can be prevented altogether, even with the most gentle care. However, it is imperative to strive for standardized NICU care guidelines to facilitate the best possible outcome and prevent long-term adverse effects.

The present study was conducted in a tertiary level neonatology that uses several developmental support practices to reduce stress (low and indirect light, covering the incubator, decreased environmental noise, supportive bedding, opportunities for gripping, and clustering medical care interventions as much as possible). Previous studies have shown that reducing stressful environmental stimuli in the NICU can reduce IH. This could be one reason for the low IH incidence during rest.

Limitations

The sample size was small but was compensated by the intraindividual study design. Observational studies are always at risk of Hawthorne effects, which we limited through blinding. Another limitation is that we did not monitor sleep states. Previous studies have shown that newborns' tolerance of handling was associated with sleep state and that IH frequency increased during awake or indeterminate sleep compared to quiet or active sleep [28].

We did not differentiate between NMC interventions (i.e., pharyngeal suctioning, blood sampling, diaper change). Therefore, we could not identify those procedures that are most likely to induce IH. Future studies should adopt appropriate clusters for stress and pain (e.g., those proposed by [23]) to uncover underlying factors of IH occurrence. It is already known that gavage feeding is associated with fewer desaturations than bottle-feeding both during and up to 2 h after the feed. In our sample, all participants were fed via an orogastric tube, and mechanically ventilated infants were excluded [26, 27]. The high incidence of IH during NMC in our sample is, therefore, not due to feeding-induced desaturations.

Conclusion

Preterm neonates experience a multitude of handling situations during their stay at the NICU with different physiologic effects. Our study shows that clinical care and incubator touch, above all other interventions, are associated with IH. More research is needed to understand how preterm infants process touch.

Acknowledgments

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Statement of Ethics

The Ethics Committee of the University of Leipzig, in compliance with the Helsinki Declaration, approved the study (reference number: 265/18-ek). We obtained written informed consent from the parents/legal guardian to participate in the study.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

All authors revised the manuscript critically for important intellectual content, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work. Martin Grunwald conceptualized and designed the study, designed data collection instruments, and coordinated and supervised data collection. Stephanie M. Mueller conceptualized the study, carried out the initial analyses, and drafted the initial manuscript. Ulrich H. Thome conceptualized and designed the study and coordinated and supervised data collection. Benjamin W. Ackermann supervised data collection, data curation, and interpretation of data. Waseem Alali, Katrin Seifert, and Alina Mohr: acquisition and curation of the data. Sven Martin designed the data collection instruments, acquisition of data, and interpretation of data.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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