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Impact of a minimal handling care protocol on intraventricular hemorrhage in preterm infants: a retrospective cohort study

Saime Sundus Uygun^{1*} , Mehmet Ozturk², Hanifi Soylu³ and Murat Konak¹

Abstract

Background Premature birth is associated with a high risk of mortality and neurodevelopmental morbidity, with intraventricular hemorrhage (IVH) remaining a major cause of brain injury in preterm infants. Neuroprotective care bundles focusing on minimal handling have been proposed to reduce physiological stress and cerebral hemodynamic instability. While such bundles have been associated with reduced rates of severe intraventricular hemorrhage, evidence regarding the isolated impact of minimal handling—particularly on other neonatal morbidities—remains limited.

Methods This retrospective comparative cohort study was conducted in a tertiary-level neonatal intensive care unit between January 2020 and December 2023. Preterm infants with a gestational age ≤ 32 weeks and birth weight ≤ 1500 g were included. Outcomes were compared between a pre-bundle period (2020–2021) and a post-bundle period (2022–2023), following the unit-wide implementation of a structured minimal handling care protocol during the first 72 h of life. The primary outcome was the incidence and severity of IVH diagnosed by cranial ultrasonography. Secondary outcomes included major neonatal morbidities and mortality. Multivariable logistic regression was used to identify independent risk factors for IVH.

Results A total of 112 infants were included (46 pre-bundle, 66 post-bundle). The overall incidence and severity distribution of IVH did not differ significantly between groups. Rates of necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity, sepsis, and mortality were also comparable. In multivariable analysis, maternal diabetes and nosocomial sepsis were identified as factors associated with IVH.

Conclusion Implementation of a minimal handling care bundle was feasible and safe in a tertiary neonatal intensive care unit. However, due to the limited sample size and low number of IVH events, its effect on the incidence and severity of IVH could not be clearly delineated.

Keywords Preterm infants, Intraventricular hemorrhage, Minimal handling, Neuroprotective care bundle, Neonatal intensive care unit

*Correspondence:

Saime Sundus Uygun

uygunsaime@hotmail.com; saimeuygun@selcuk.edu.tr

¹Department of Neonatology, Selçuk University Faculty of Medicine, Konya, Turkey

²Department of Pediatric Radiology, Selçuk University Faculty of Medicine, Konya, Turkey

³Division of Neonatology, University of Manitoba & Shared Health, Winnipeg, MB, Canada



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Background

Premature birth, which is defined by the World Health Organization (WHO) as delivery before 37 weeks of gestation, is one of the leading causes of neonatal mortality and morbidity worldwide [1] and remains a major public health concern [2]. Premature infants are vulnerable to a wide range of complications, including respiratory distress syndrome, chronic lung disease, infections, and neurological injury [3]. The risk of adverse outcomes increases markedly with decreasing gestational age [4].

Intraventricular haemorrhage (IVH) is a major cause of cerebral injury in preterm infants, particularly those with very low birth weight [5]. IVH is a complex condition that predominantly affects infants born before 32 weeks of gestation [6]. The haemorrhage originates from the germinal matrix (GM), a highly vascularized region rich in glial and neural precursor cells [7]. This fragile structure persists until approximately 33 weeks of gestation [8] and, due to immature cerebral autoregulation, is highly susceptible to fluctuations in cerebral blood flow [9]. Severe IVH (grades III–IV) is strongly associated with post-hemorrhagic hydrocephalus (PHH), periventricular leukomalacia (PVL), and long-term neurodevelopmental impairment, as well as increased mortality [10]. IVH most commonly occurs within the first week of life, with most cases developing within the first 72 h. The risk is particularly high in extremely preterm infants (< 28 weeks of gestation), in whom the fragility of the germinal matrix and the immaturity of cerebral autoregulation further increase susceptibility [11, 12]. These observations underscore the critical importance of early neuroprotective strategies during the immediate postnatal period.

Following birth, premature infants are abruptly exposed to multiple environmental stressors in the Neonatal Intensive Care Unit (NICU), including noise, light, and temperature instability [13]. These stressors may disrupt physiological stability and contribute to adverse neurological and cognitive outcomes [14, 15]. To mitigate these effects, the Individualized Developmental Care (IDC) model was introduced in the 1980s [16]. The core principle of this model is clustered care, in which routine care procedures are grouped into defined periods to minimize handling and allow prolonged uninterrupted rest [17]. Clustered care has been associated with favorable physiological effects, such as reduced apnea frequency, lower oxygen requirements, and improved weight gain [18]. Neuroprotective care bundles incorporate these principles while additionally aiming to optimize cerebral venous drainage through strategies such as neutral head positioning and avoidance of abrupt postural changes [19].

Previous studies have demonstrated that neuroprotective care bundles emphasizing minimal handling are associated with reduced incidence and severity of IVH

in preterm infants [20]. Advances in perinatal and neonatal care have decreased IVH rates from historical levels of 40–50% to approximately 20–25% in very low birth weight infants [21]. Nevertheless, as survival among extremely preterm infants continues to improve, concerns regarding persistent neurodevelopmental impairment remain substantial [22]. Most available studies have focused primarily on IVH outcomes, with limited evaluation of the broader impact of care bundles on other neonatal morbidities. Moreover, the effectiveness of such bundles depends heavily on staff adherence, structured training, and institutional commitment [23]. Improved compliance has been linked to lower rates of severe IVH, underscoring the importance of standardized implementation and continuous auditing tools [24].

Therefore, the primary objective of this study was to evaluate the impact of a minimal handling care bundle implemented in our NICU on the incidence, severity, and clinical correlates of IVH in preterm infants by comparing outcomes between a pre-bundle period (2020–2021) and a post-bundle period (2022–2023). In addition, we assessed the association between bundle implementation and other major early and late neonatal morbidities, including sepsis, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, hemodynamically significant patent ductus arteriosus, and mortality. Given the quality improvement nature of the intervention, any observed differences were interpreted as associations rather than causal effects.

Materials and methods

Study design and setting

This retrospective, comparative cohort study was conducted in the Neonatal Intensive Care Unit of Selçuk University Faculty of Medicine Hospital, a tertiary-level referral center in Konya, Turkey, between 1 January 2020 and 31 December 2023. The study population included preterm infants born at < 32 weeks' gestation and admitted to the NICU during the study period. The gestational age threshold (≤ 32 weeks) was selected to reflect the standard definition of very preterm infants and to represent real-world NICU practice.

In January 2022, a structured minimal handling care bundle protocol was implemented unit wide as part of routine neuroprotective care. Accordingly, infants were categorized into two cohorts based on the timing of birth relative to protocol implementation. The pre-bundle group included infants born and managed between January 2020 and December 2021, whereas the post-bundle group comprised infants born and managed between January 2022 and December 2023. Both cohorts were managed by the same multidisciplinary clinical team, and the unit's general treatment policies remained consistent

throughout the study period, except for the introduction of the minimal handling protocol.

The primary objective of the study was to compare the incidence and severity of intraventricular hemorrhage between the pre-bundle and post-bundle cohorts. Secondary outcomes included other prematurity-associated neonatal morbidities. Clinical outcomes were compared between groups to assess the association between protocol implementation and neonatal outcomes.

Study population

A total of 112 preterm infants with a gestational age ≤ 32 weeks and birth weight ≤ 1500 g were included. Infants were categorized into a pre-bundle group (January 2020–December 2021) and a post-bundle group (January 2022–December 2023). There were 46 infants in the pre-bundle group and 66 in the post-bundle group. Infants who died before completion of cranial ultrasonography were excluded from morbidity-specific analyses due to unavailable outcome data.

Exclusion criteria included the following:

- Major congenital anomalies.
- Severe perinatal asphyxia.
- Missing cranial ultrasonography (cUSG) data.
- Death before completion of cranial ultrasonography.
- Outborn infants referred from external centers.

Data collection

The following data were collected from medical records:

Demographic parameters included gestational age, birth weight, mode of delivery, sex, and multiple gestation.

Antenatal variables included complete antenatal corticosteroid exposure, maternal age, maternal diabetes mellitus, pre-eclampsia, and premature rupture of membranes (PROM).

Early and late neonatal morbidities included early-onset sepsis; late-onset (nosocomial) sepsis; respiratory distress syndrome (RDS) requiring surfactant therapy; retinopathy of prematurity (ROP) grade ≥ 2 ; necrotizing enterocolitis (NEC) stage ≥ 2 ; hemodynamically significant patent ductus arteriosus (hsPDA); bronchopulmonary dysplasia (BPD); intraventricular hemorrhage (IVH); and mortality.

Additional evaluations were performed for infants diagnosed with IVH to determine hemorrhage grade and the need for neurosurgical interventions, including external ventricular drainage (EVD) and/or ventriculoperitoneal (VP) shunt placement.

Minimal handling care bundle protocol

To enhance neuroprotective care in premature infants, a structured minimal handling care bundle targeting the first 72 h of life was implemented in the unit. The bundle consisted of complementary interventions designed to reduce physiological stress, minimize cerebral hemodynamic fluctuations, and limit unnecessary sensory stimulation.

The core components of the bundle included:

1. Clustering care procedures and minimizing handling.
2. Reducing environmental noise and light exposure.
3. Maintaining a calm and protective environment.
4. Ensuring strict midline head positioning.
5. Turning the head and trunk together as a single unit during repositioning.
6. Avoiding sudden postural changes.
7. Performing all procedures gently with minimal sensory input.

During the first 72 h of life, infants were protected from unnecessary handling and routine weighing was avoided. Fluid management was individualized based on urine output and the presence of edema, with diapers assessed twice daily and overall fluid balance closely monitored.

Vital signs were monitored using minimally invasive methods whenever possible, including pulse oximetry for oxygen saturation, skin probes for temperature monitoring, and arterial blood pressure measurement when arterial access was available. To further reduce physiological stress, no skin care interventions such as moisturization or massage were performed during this period. Incubators were covered with noise- and light-reducing covers, and invasive procedures were scheduled within clustered care times to limit unnecessary contact.

All bundle components were standardized through unit-wide training sessions prior to implementation. Adherence to the protocol was supported through ongoing staff education and monitored by senior clinicians during routine clinical practice throughout the study period.

Study outcomes

The primary outcome of this study was the incidence and severity of IVH, diagnosed and graded using routine cranial ultrasonography (cUSG) during NICU hospitalization.

The secondary outcomes included:

- Mortality during hospitalization.
- Sepsis (early-onset and nosocomial).
- Necrotizing enterocolitis (NEC) stage ≥ 2 .

- Hemodynamically significant patent ductus arteriosus (hsPDA) requiring medical or surgical treatment.
- Bronchopulmonary dysplasia (BPD), categorized as mild, moderate, or severe according to oxygen requirements.
- Retinopathy of prematurity (ROP), including the need for anti-VEGF therapy or laser treatment.
- Requirement for red blood cell transfusion.

Definitions

Complete antenatal steroid exposure was defined as receipt of two doses of betamethasone (or an equivalent regimen) administered at least 24 h prior to delivery. Maternal conditions, including preeclampsia, maternal diabetes, and premature rupture of membranes, were recorded based on obstetric diagnoses documented in the maternal medical record.

Early-onset sepsis (EOS) was defined as culture-proven or clinically suspected infection occurring within the first 72 h of life. Late-onset (nosocomial) sepsis (LOS) was defined as sepsis occurring after 72 h of life, based on clinical signs and laboratory findings consistent with infection.

Necrotizing enterocolitis (NEC) stage ≥ 2 was defined according to the modified Bell's criteria. Hemodynamically significant patent ductus arteriosus (hsPDA) was diagnosed based on combined clinical and echocardiographic criteria.

Bronchopulmonary dysplasia (BPD) and its severity (none, mild, moderate, or severe) were defined according to the NICHD consensus criteria at 36 weeks postmenstrual age. Infants who died before 36 weeks PMA were classified as "not assessable" and excluded from BPD outcome analyses.

Retinopathy of prematurity (ROP) was classified based on treatment requirements. For infants requiring intervention, the type of therapy (laser photocoagulation or intravitreal anti-VEGF injection) was recorded. Infants who died before ophthalmologic evaluation were categorized as "not assessable."

Cranial ultrasonography was performed and interpreted by experienced pediatric radiologists according to standardized institutional protocols and graded using the Papile classification (grades I–IV). For infants with IVH, any neurosurgical intervention—including external ventricular drainage (EVD) or ventriculoperitoneal (VP) shunt placement—was recorded.

Red blood cell transfusion outcomes were evaluated for infants surviving long enough for transfusion assessment. Infants who died before transfusion evaluation were categorized as "not assessable."

Follow-up

All infants were monitored throughout their NICU stay using standardized clinical protocols.

Follow-up assessments included:

- Cranial ultrasonography performed at regular intervals to assess the presence and severity of IVH.
- Clinical monitoring for signs of sepsis, PDA, and NEC.
- Respiratory follow-up to evaluate the development and severity of BPD.
- Ophthalmologic screening for ROP staging and treatment decisions.
- Documentation of transfusion requirements and survival status at discharge.

Follow-up was completed until NICU discharge or death.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed variables were expressed as mean $\pm$ standard deviation and compared using the independent samples t-test. Non-normally distributed variables were expressed as median (interquartile range) and compared using the Mann–Whitney U test.

Categorical variables were presented as frequencies (percentages) and compared using the chi-squared test or Fisher's exact test, as appropriate.

Subgroup analyses were performed according to IVH severity grades. Logistic regression analysis was used to explore factors associated with IVH and other major morbidities. Variables considered clinically relevant were included in the regression models, taking into account both statistical and biological plausibility. Given the limited number of events, regression analyses were considered exploratory.

A p-value of <0.05 was considered statistically significant.

Ethical approval

Ethical approval was obtained from the Local Ethics Committee of the Dean's Office of Selçuk University Faculty of Medicine (decision number 2023/193). The study was conducted in accordance with the Declaration of Helsinki and relevant local regulations. Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

Table 1 Demographic data of patients included in the study

Variable	Category	Pre-Bundle n (%)	Post-Bundle n (%)	Total n (%)
Sex	Male	23 (50.0%)	39 (59.1%)	62 (55.4%)
	Female	23 (50.0%)	27 (40.9%)	50 (44.6%)
Gestational age (weeks)	< 28 weeks	22 (47.8%)	31 (47.0%)	53 (47.3%)
	28–30 weeks	11 (23.9%)	20 (30.3%)	31 (27.7%)
	30–32 weeks	9 (19.6%)	15 (22.7%)	24 (21.4%)
	32–36 weeks	1 (2.2%)	1 (1.5%)	2 (1.8%)
Mode of Delivery	VD	11 (23.9%)	15 (22.7%)	26 (23.2%)
	C/S	35 (76.1%)	51 (77.3%)	86 (76.8%)
Multiple gestation	No	43 (93.5%)	50 (75.8%)	93 (83.0%)
	Yes	3 (6.5%)	16 (24.2%)	19 (17.0%)
Full-dose antenatal steroid	No	17 (37.0%)	18 (27.3%)	35 (31.3%)
	Yes	29 (63.0%)	48 (72.7%)	77 (68.8%)
Preeclampsia in mothers	No	28 (60.9%)	50 (75.8%)	78 (69.6%)
	Yes	18 (39.1%)	16 (24.2%)	34 (30.4%)
Maternal diabetes	No	45 (97.8%)	62 (93.9%)	107 (95.5%)
	Yes	1 (2.2%)	4 (6.1%)	5 (4.5%)
PROM	No	27 (58.7%)	39 (59.1%)	66 (58.9%)
	Yes	19 (41.3%)	27 (40.9%)	46 (41.1%)
Delivery room resuscitation	CPAP	34 (73.9%)	52 (78.8%)	86 (76.8%)
	Intubation	12 (26.1%)	14 (21.2%)	26 (23.2%)
EOS	No	46 (100%)	58 (87.9%)	104 (92.9%)
	Yes	0 (0%)	8 (12.1%)	8 (7.1%)
Nosocomial sepsis	No	22 (47.8%)	38 (57.6%)	60 (53.6%)
	Yes	24 (52.2%)	28 (42.4%)	52 (46.4%)

Descriptive comparisons are presented without statistical testing, as recommended for baseline characteristics in observational studies

Distribution of gestational age categories is presented to better reflect baseline IVH risk

VD Vaginal Delivery, C/S Cesarean section, PROM Premature rupture of membranes, CPAP Continuous positive airway pressure, EOS Early-Onset Neonatal Sepsis

Results

A total of 112 infants were included in the study: 46 in the pre-bundle group and 66 in the post-bundle group. The median gestational age of the cohort was 29 weeks (IQR 27–31), and the median birth weight was 1250 g (IQR 950–1450). Demographic characteristics are summarized in Table 1.

There were no significant differences between groups in terms of sex, mode of delivery, antenatal steroid exposure, maternal pre-eclampsia, maternal diabetes, or premature rupture of membranes. However, multiple gestation was more frequent in the post-bundle group than in the pre-bundle group (16 vs. 3, $p=0.011$). The incidence of early-onset sepsis was also higher in the post-bundle group (8 vs. 0, $p=0.012$). No significant

Table 2 Clinical outcomes and follow-up data

Variable	Category	Pre-bundle n (%)	Post-bundle n (%)	Total n (%)
Intracranial hemorrhage and hemorrhage stage	No	34 (73.9%)	51 (77.3%)	85 (75.9%)
	Stage 1	5 (10.9%)	9 (13.6%)	14 (12.5%)
	Stage 2	5 (10.9%)	4 (6.1%)	9 (8.0%)
	Stage 3	1 (2.2%)	1 (1.5%)	2 (1.8%)
	Stage 4	1 (2.2%)	1 (1.5%)	2 (1.8%)
Neurosurgical intervention for IVH	EVD	1 (2.2%)	1 (1.5%)	2 (1.8%)
	VP shunt	1 (2.2%)	2 (3.0%)	3 (2.7%)
NEC Stage 2 and higher	No	38 (82.6%)	53 (80.3%)	91 (81.2%)
	Yes	8 (17.4%)	11 (16.7%)	19 (17.0%)
Number of red blood cell transfusions	0	16 (34.8%)	21 (31.8%)	37 (33.0%)
	1	10 (21.7%)	11 (16.7%)	21 (18.8%)
	2	4 (8.7%)	14 (21.2%)	18 (16.1%)
	3 +	14 (30.4%)	18 (27.3%)	32 (28.6%)
BPD and BPD severity	No	21 (45.7%)	27 (40.9%)	48 (42.9%)
	Mild	4 (8.7%)	6 (9.1%)	10 (8.9%)
	Moderate	10 (21.7%)	15 (22.7%)	25 (22.3%)
	Severe	9 (19.6%)	16 (24.2%)	25 (22.3%)
	Not assessable	2 (4.3%)	2 (3.0%)	4 (3.6%)
Treatment requiring ROP and treatment type	No	37 (80.4%)	55 (83.3%)	92 (82.1%)
	LPC	6 (13.0%)	6 (9.1%)	12 (10.7%)
	Anti-VEGF	1 (2.2%)	3 (4.5%)	4 (3.6%)
Hemodynamically significant PDA and treatment type	No	33 (71.7%)	45 (68.2%)	78 (69.6%)
	Yes	13 (28.3%)	21 (31.8%)	34 (30.4%)
	Medical closure	9 (19.6%)	21 (31.8%)	30 (26.8%)
	Surgical ligation	4 (8.7%)	0 (0.0%)	4 (3.6%)
Mortality	No	38 (82.6%)	58 (87.9%)	96 (85.7%)
	Yes	8 (17.4%)	8 (12.1%)	16 (14.3%)

Most infants requiring VP shunt placement had previously undergone EVD; however, in one case in the post-bundle group, VP shunt placement was performed without prior EVD

Statistical comparisons for neurosurgical intervention outcomes (EVD and VP shunt) were not performed due to the very low number of events

Not assessable: infants who died before 36 weeks postmenstrual age and therefore could not be evaluated for BPD

Some infants who died before completion of follow-up could not be evaluated for certain outcomes (including ROP and transfusion-related outcomes)

No statistically significant differences were observed between the pre-bundle and post-bundle groups for any of the variables presented

EVD External ventricular drain, VP shunt Ventriculoperitoneal shunt, NEC Necrotizing enterocolitis, BPD Bronchopulmonary dysplasia, ROP Retinopathy of prematurity, LPC Laser Photocoagulation, Anti-VEGF Anti-vascular endothelial growth factor, PDA Patent ductus arteriosus

differences were observed in delivery room resuscitation or nosocomial sepsis between groups.

Clinical outcomes and follow-up findings are summarized in Table 2. No statistically significant differences were observed in the overall incidence or severity distribution of intraventricular haemorrhage between the groups. Neurosurgical interventions (EVD and/or VP shunt) were rare in both groups. Most infants requiring

VP shunt placement had previously undergone EVD; one infant in the post-bundle group received a VP shunt without prior EVD. The incidence of necrotizing enterocolitis stage ≥ 2 was similar between the pre- and post-bundle groups (8 vs. 12, $p=0.561$). Similarly, the requirement for red blood cell transfusion did not differ significantly between groups ($p=0.257$).

The occurrence of bronchopulmonary dysplasia was comparable between the groups ($p=0.355$). Similarly, the rate of treatment-requiring retinopathy of prematurity (ROP) did not differ between groups, and treatment modalities were comparable. Overall mortality occurred in 16 infants and was equally distributed between the pre- and post-bundle groups (8 vs. 8, $p=0.303$). hsPDA was identified in 34 infants, with no significant difference in overall incidence between the groups ($p=0.425$). However, surgical ligation for hsPDA was observed only in the pre-bundle group (4 vs. 0, $p=0.026$).

Univariable analyses were initially performed to explore factors associated with intraventricular haemorrhage. Variables considered clinically relevant were subsequently included in the multivariable logistic regression model. Candidate variables included maternal diabetes, multiple gestation, NEC stage ≥ 2 , BPD, ROP requiring treatment, hsPDA, nosocomial sepsis, birth weight, and gestational age.

In the multivariable model, maternal diabetes and nosocomial sepsis were associated with IVH (Table 3). Maternal diabetes was associated with increased odds of IVH (odds ratio [OR] ≈ 22.6 , $p=0.014$), and nosocomial sepsis was also associated with higher risk (OR ≈ 6.1 , $p=0.005$). Although lower gestational age and birth weight were associated with IVH in univariable analyses, these associations did not persist after multivariable adjustment.

As only four infants developed severe IVH (grades III–IV), subgroup analyses according to haemorrhage severity were not performed due to limited statistical power.

Discussion

This retrospective cohort study evaluated the impact of a structured minimal handling care bundle on IVH and major neonatal morbidities. In our cohort, implementation of the bundle was not associated with a significant reduction in the incidence or severity of IVH. While previous studies have reported beneficial effects of comprehensive neuroprotective bundles [25], our findings suggest that minimal handling alone may not be sufficient to meaningfully influence IVH outcomes.

The scope and intensity of the intervention in our study differed from those of previously published neuroprotective bundle studies. Investigations by Mohammad et al., Tang et al., and Benlamri et al. demonstrated significant reductions in severe brain injury using multimodal

Table 3 Multivariable logistic regression analysis of factors associated with IVH

Variable	OR	95% CI (Lower–Upper)	p-value	Interpretation
Maternal diabetes	22.6	1.9–273.6	0.014	Associated with IVH
Nosocomial sepsis	6.1	1.7–21.4	0.005	Associated with IVH
NEC $\geq$ Stage 2	3.0	0.9–9.9	0.074	Not statistically significant

strategies that combined standardized head positioning, meticulous hemodynamic management, respiratory optimization, structured staff training, and continuous feedback mechanisms [26–28]. In contrast, our intervention focused primarily on reduced handling, environmental modification, and head midline stabilization during the first 72 h of life. Although these measures promote physiological stability, they do not encompass the full spectrum of interventions included in more comprehensive neuroprotection programs, which are likely to explain the more modest impact observed in our study.

In this study, we evaluated a broad range of neonatal morbidities beyond IVH, including NEC, BPD, ROP, sepsis, and PDA. This approach allows for a more comprehensive assessment of the potential clinical effects of minimal handling strategies compared to studies focusing solely on IVH outcomes and may help clarify which aspects of neonatal care are more likely to be influenced by such interventions.

Maternal diabetes and nosocomial sepsis were identified as factors associated with IVH in our cohort. Although these findings are consistent with previous studies suggesting that metabolic disturbances and systemic inflammation may affect cerebral autoregulation, they should be interpreted with caution given the limited number of cases [29]. These associations should therefore be considered exploratory rather than definitive. The wide confidence interval observed for maternal diabetes likely reflects the small number of exposed cases. Additionally, the higher prevalence of early-onset sepsis and multiple gestation in the post-bundle group may have acted as confounding factors and should be considered when interpreting the results.

Given the limited number of IVH events, the regression analysis may be underpowered and susceptible to overfitting. Therefore, the findings from multivariable analysis should be interpreted with caution. In addition, the selection of variables for the multivariable model may not fully account for biological plausibility and temporal relationships. Some variables included in the analysis, such as NEC, ROP, and BPD, typically occur later in the clinical course and are therefore unlikely to act as confounders for early IVH outcomes.

Several explanations may account for the absence of a significant reduction in IVH incidence. IVH is a multifactorial condition influenced by gestational age, birth weight, hemodynamic instability, ventilatory strategies, inflammatory processes, and genetic susceptibility. While minimal handling may reduce stress-related physiological fluctuations, it is unlikely to sufficiently modify the complex cerebral hemodynamic mechanisms underlying IVH when applied in isolation. The retrospective design also limited the assessment of detailed physiological parameters such as blood pressure variability, cerebral blood flow dynamics, and ventilatory settings. Differences in baseline characteristics between groups further complicate interpretation of the intervention's effect.

In addition, the gestational age distribution of the study population may have influenced the observed results. As the risk of IVH is substantially lower in more mature preterm infants, a cohort including a higher proportion of infants closer to 30–32 weeks of gestation may have had a lower baseline risk of IVH. This may have limited the ability to detect a measurable effect of intervention. Furthermore, the relatively small number of extremely preterm infants in the cohort may have limited the overall incidence of IVH, thereby reducing the ability to detect a significant effect of the intervention. In addition, the very low incidence of severe IVH in both groups may have further limited the ability to detect differences between cohorts, particularly for clinically significant outcomes.

A noteworthy finding of our study was the reduction in the rate of surgical ligation for hsPDA during the post-bundle period. However, this finding should be interpreted with caution. Changes in clinical practice related to PDA diagnosis and management over time, as well as unmeasured confounding factors, may have contributed to this observation. Although reduced handling may theoretically support hemodynamic stability, this relationship remains speculative in the context of the present study, particularly given the similar number of PDA cases and medical treatment rates between groups. Given the retrospective, single-center observational design, these findings should be interpreted as associations rather than causal relationships.

In our study population, minimal handling alone was not associated with a reduction in IVH. These findings suggest that integration of minimal handling practices into comprehensive, multimodal neuroprotective care bundles may be necessary to achieve meaningful improvements in outcomes.

Limitations

This study has several important limitations, most notably the relatively small sample size and the low number of IVH events, which limit statistical power and the ability to detect meaningful differences between groups. The

low event rate also restricted the robustness of subgroup and multivariable analyses and may have increased the risk of overfitting.

Although early-onset sepsis and multiple gestation were more prevalent in the post-bundle group, residual confounding related to other maternal, perinatal, or clinical factors cannot be fully excluded. Despite multivariable adjustment, unmeasured confounders may have influenced the observed associations.

Third, detailed physiological parameters closely linked to IVH pathophysiology—such as blood pressure variability, blood gas fluctuations, and indices of cerebral autoregulation—were not available due to the retrospective design, precluding a more detailed mechanistic assessment.

Fourth, as this was a single-center study, the generalizability of the findings to other NICU settings with different patient populations, resources, and care practices may be limited.

The inclusion of infants with relatively higher gestational ages may have reduced the baseline risk of IVH and potentially diluted any measurable effect of the intervention. As IVH is more common in extremely preterm infants, this may have limited the ability to detect differences between groups. Subgroup analyses according to gestational age were not feasible due to the limited sample size.

Although cranial ultrasonography was performed according to standardized institutional protocols, examinations were interpreted by different clinicians, and inter-observer variability cannot be excluded.

Two infants in the pre-bundle group and two infants in the post-bundle group died before completion of cranial ultrasonography and were therefore excluded from morbidity-specific analyses. As IVH status could not be confirmed in these cases, undiagnosed IVH cannot be excluded. This may have introduced potential bias and should be considered when interpreting the results.

Conclusion

In conclusion, implementation of a minimal handling care bundle in a tertiary neonatal intensive care unit was feasible. However, due to the limited sample size, low number of IVH events, and heterogeneous study population, the effect of the intervention on IVH could not be clearly delineated. In our study population, minimal handling alone was not associated with a reduction in IVH. These findings suggest that integration of minimal handling into broader, multimodal neuroprotective strategies may be necessary to achieve meaningful improvements in outcomes. Further prospective, multicenter studies are needed to better define the role of minimal handling within comprehensive neuroprotective care.

Abbreviations

WHO	World Health Organization
IVH	Intraventricular hemorrhage
GM	Germinal matrix
PHH	Post-hemorrhagic hydrocephalus
PVL	Periventricular leukomalacia
NICU	Neonatal intensive care unit
IDC	Individualized Developmental Care
cUSG	Cranial ultrasonography
PROM	Premature rupture of the membranes
RDS	Respiratory distress syndrome
NEC	Necrotizing enterocolitis
hsPDA	Haemodynamically significant patent ductus arteriosus
BPD	Bronchopulmonary dysplasia
VEGF	Vascular Endothelial Growth Factor
EOS	Early-onset sepsis
LOS	Late-onset (nosocomial) sepsis
ROP	Retinopathy of prematurity
PDA	Patent ductus arteriosus
hsPDA	Hemodynamically significant patent ductus arteriosus
EOS	Early-onset sepsis
LOS	Late-onset sepsis
cUSG	Cranial ultrasonography
EVD	External ventricular drainage
VP	Ventriculoperitoneal
VD	Vaginal Delivery
C/S	Cesarean section
CPAP	Continuous positive airway pressure
LPC	Laser Photocoagulation
VP shunt	Ventriculoperitoneal shunt

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Authors' contributions

Saime Sundus Uygun conceptualized and designed the study, coordinated data collection, interpreted the data, and drafted the manuscript. Murat Konak performed the statistical analyses and contributed to data interpretation. Mehmet Öztürk conducted the radiological evaluations and contributed to the interpretation of imaging findings. Hanifi Soyulu contributed to study design, provided critical language editing, and revised the manuscript for important intellectual content. All authors read and approved of the final manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Local Ethics Committee of the Dean's Office of Selçuk University Faculty of Medicine (Decision No: 2023/193, Meeting Date: 11 April 2023). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Due to the retrospective nature of the study, the requirement for informed consent was waived by the Local Ethics Committee of the Dean's Office of Selçuk University Faculty of Medicine. Nevertheless, written informed consent to participate was obtained from the parents/legal guardians of the patients included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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