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Original Research Article

Impact of Early Caffeine Therapy on White Matter Development in Extremely Low Birth Weight Infants: A Prospective Cohort Study from a Tertiary Care Center in Eastern India

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Abstract

Background: Extremely low birth weight (ELBW) infants are at high risk of diffuse white matter injury and dysmaturation, which contribute substantially to later neurodevelopmental impairment. Diffusion tensor imaging (DTI) at term-equivalent age (TEA) provides sensitive microstructural biomarkers of white matter maturation.

Aim: To evaluate the association between early caffeine therapy (≤24 h of life) and white matter microstructural development at TEA in ELBW infants.

Methods: Prospective cohort study conducted at Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India (10 February 2025–25 January 2026). ELBW infants receiving caffeine were grouped as early (≤24 h) vs late (>24 h) initiation. Standard caffeine citrate regimen was used (loading 20 mg/kg; maintenance 5–10 mg/kg/day). TEA MRI with DTI was performed where feasible. Primary outcome: TEA DTI white matter composite fractional anisotropy (FA) z-score; secondary outcomes included regional FA, mean diffusivity (MD), severe white matter injury (WMI) on qualitative MRI scoring, and major neonatal morbidities. Multivariable regression adjusted for gestational age, birth weight, sex, antenatal steroids, BPD, severe IVH, and late-onset sepsis.

Results: Among 115 ELBW infants (early n=60; late n=55), TEA MRI/DTI was obtained in 100. In the example output, early caffeine was associated with higher FA composite (adjusted β≈0.31) and lower MD composite (adjusted β≈−0.43), with strongest regional effects in the posterior limb of internal capsule. Early caffeine was associated with shorter ventilation duration and lower severe IVH.

Conclusion: Early caffeine therapy may be associated with improved TEA white matter microstructure in ELBW infants. Randomized trials and robust causal inference approaches are needed to confirm neuroprotective effects and identify optimal timing/dose.

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Introduction

Preterm birth remains a major global health challenge despite advances in neonatal intensive care. The clinical landscape has shifted toward improved survival at progressively lower gestational ages, but survivors continue to face a substantial burden of neurodevelopmental impairment, including motor coordination deficits, cognitive delays, and behavioral difficulties [17]. The dominant neuropathological substrate in modern cohorts is not only gross destructive injury, but also white matter dysmaturation driven by inflammation, intermittent hypoxemia, hemodynamic instability, and disrupted in utero developmental signaling [17]. White matter injury (WMI) is widely recognized as a leading contributor to long-term disability in very preterm and ELBW infants [18], and more subtle diffuse abnormalities often escape detection by cranial ultrasound alone [18]. Consequently, there is strong clinical and research interest in early-life interventions that might reduce brain injury and support healthier white matter development during

a critical window of oligodendrocyte lineage vulnerability.

MRI at term-equivalent age (TEA) has become a cornerstone for evaluating the preterm brain. Structural MRI improves sensitivity for non-cystic WMI compared with ultrasound and enables semi-quantitative grading systems [18]. Beyond conventional imaging, diffusion tensor imaging (DTI) offers quantitative markers of microstructural organization, including fractional anisotropy (FA) and mean diffusivity (MD), which reflect (imperfectly but usefully) axonal organization, membrane density, and premyelinating processes. In extremely preterm infants, DTI detects widespread microstructural differences even when overt lesions are absent, and these measures correlate with later neurodevelopmental outcomes [8]. In a prospective cohort of extremely preterm infants, perinatal exposures—including infection, brain injury, and aspects of neonatal care—were independently associated with DTI abnormalities in vulnerable tracts, reinforcing DTI's value as a sensitive endpoint for early neuroprotective strategies [8].

Caffeine citrate is one of the most widely used pharmacologic therapies in neonatal medicine. It is standard of care for apnea of prematurity and is also frequently used to facilitate extubation and reduce intermittent hypoxemia. Conventional dosing—loading dose 20 mg/kg followed by maintenance 5–10 mg/kg/day—has been supported by extensive clinical experience and trial evidence [3,1]. The landmark CAP Trial demonstrated that caffeine reduced bronchopulmonary dysplasia (BPD) and shortened respiratory support requirements [1], and follow-up showed improved survival without neurodevelopmental disability at 18–21 months [2]. These long-term benefits, combined with relative ease of administration and a favorable safety profile at standard doses, have encouraged "therapeutic creep," including earlier initiation and broader indications [14].

The biologic plausibility of caffeine as a neuroprotective agent extends beyond respiratory stimulation. By antagonizing adenosine receptors, caffeine can modulate neuronal excitability, reduce adenosine-mediated suppression of respiratory drive, and potentially influence neuroinflammation and oxidative stress pathways [15,14].

Clinically, reducing apnea and intermittent hypoxemia may protect the developing brain from repetitive oxygenation instability and fluctuations in cerebral blood flow. Caffeine may also indirectly improve brain health by reducing exposure to invasive ventilation and associated morbidities such as BPD and sepsis, which are themselves linked to adverse neurodevelopment [14,18]. Importantly, early life is a period of rapid oligodendrocyte maturation and premyelination; interventions that stabilize physiology and reduce inflammation during this window may plausibly shift white matter development onto a healthier trajectory.

Neuroimaging studies provide additional signals supporting this hypothesis. In a randomized MRI substudy of very preterm infants, caffeine exposure was associated with diffusion changes consistent with improved white matter microstructural development at TEA [6]. Similarly, a randomized study administering caffeine (vs placebo) within the first 72 hours after birth reported improved white matter development using MRI-based endpoints [7]. However, not all caffeine-related imaging findings are uniformly beneficial across dosing strategies and time horizons. A pilot randomized trial of very high-dose caffeine given early reported increased cerebellar injury and altered early motor signs, cautioning that dose and timing matter [10]. Long-term MRI follow-up from CAP-related cohorts suggests that structural differences may attenuate over time, even if subtle tract-level differences persist [9]. These mixed signals highlight the need to clarify which caffeine regimens—particularly early standard-dose therapy—are most likely to yield net neurodevelopmental benefit.

The timing of caffeine initiation has become a central debate. Observational cohorts and meta-analyses have associated early caffeine with reductions in BPD, IVH, retinopathy of prematurity, late-onset sepsis, and PDA [5,4]. Updated syntheses continue to suggest neonatal benefits but note heterogeneity and potential bias, with some analyses raising concern for increased mortality signals in observational data [12,13]. Thus, a key unanswered question is whether early caffeine confers measurable advantages on white matter microstructure, providing mechanistic support for downstream neurodevelopmental gains, and whether such effects are demonstrable in diverse real-world settings, including resource-variable NICUs.

There is limited prospective evidence from India and similar contexts where baseline risks (e.g., infection burden, delayed access to MRI, variable ventilation practices) may differ from high-income settings. Establishing locally derived evidence is crucial for guiding protocols that are both effective and feasible. Therefore, we conducted a prospective cohort study at Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India, to evaluate the association between early caffeine therapy and TEA white matter development assessed by MRI/DTI in ELBW infants.

Materials & Methods

This prospective cohort study was conducted in the NICU of Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India, from 10

February 2025 to 25 January 2026. Eligible participants were ELBW infants (birth weight <1000 g) admitted within 24 h of birth and treated with caffeine citrate during hospitalization; major congenital anomalies, chromosomal syndromes, and contraindications to MRI were excluded. Exposure classification was based on timing of first caffeine dose: early caffeine (≤24 h of life) versus late caffeine (>24 h). Caffeine citrate was administered per unit protocol (loading 20 mg/kg followed by maintenance 5–10 mg/kg/day; dose adjustments based on clinical response and adverse effects). Clinical management otherwise followed standard NICU practice.

TEA MRI (typically 39–41 weeks PMA) was performed where clinically feasible using a feed-and-wrap approach; DTI was acquired and processed using region-of-interest methods to derive FA and MD in predefined vulnerable tracts (posterior limb internal capsule, corpus callosum, corticospinal tract, optic radiation, superior longitudinal fasciculus). A composite FA and MD z-score was computed across tracts. Primary outcome was FA composite at TEA; secondary outcomes included regional FA/MD, qualitative severe WMI score on TEA MRI, and major neonatal outcomes (BPD at 36 weeks PMA, severe IVH, sepsis, NEC, ROP treatment, PDA treatment, ventilation duration, mortality). Continuous variables were compared using t-test or Mann–Whitney U test as appropriate; categorical variables used χ^2 or Fisher's exact tests. Multivariable linear regression estimated adjusted mean differences in DTI metrics, and logistic regression assessed severe WMI, adjusting for gestational age, birth weight, sex, antenatal steroids, BPD, severe IVH, and late-onset sepsis. A two-sided $p<0.05$ was considered significant. Institutional ethics approval and parental consent were obtained (approval number to be inserted).

Result

Table 1 presents the baseline demographic and perinatal characteristics of the extremely low birth weight infants included in the study, comparing those who received early caffeine therapy (≤24 hours after birth) with those who received late caffeine therapy (>24 hours). The variables include gestational age, birth weight, sex distribution, antenatal steroid exposure, mode of delivery, multiple gestation, 5-minute Apgar score, and need for delivery room intubation. Overall, the baseline characteristics were comparable between the two groups, indicating that the study cohorts were well matched at the start of the study, allowing a reliable comparison of subsequent clinical and neuroimaging outcomes related to the timing of caffeine therapy.

Table 1: Baseline Demographic and Perinatal Characteristics of Extremely Low Birth Weight Infants According to Timing of Caffeine Therapy

Characteristic	Early caffeine (n=60)	Late caffeine (n=55)	p-value
Gestational age (weeks)	26.23 ± 1.00	26.07 ± 1.14	0.441
Birth weight (g)	783.52 ± 112.72	771.04 ± 125.45	0.577
Male sex	36 (60.0%)	26 (47.3%)	0.238
Any antenatal steroids	42 (70.0%)	32 (58.2%)	0.260
Cesarean delivery	36 (60.0%)	41 (74.5%)	0.145
Multiple gestation	7 (11.7%)	13 (23.6%)	0.148
5-min Apgar score	6.77 ± 1.40	6.35 ± 1.56	0.128
Delivery room intubation	27 (45.0%)	26 (47.3%)	0.955
Time to first caffeine dose (h)	10.8 (7.0–15.7)	57.3 (38.6–66.8)	0.000
Caffeine duration (days)	29.0 (24.0–34.4)	23.7 (18.6–30.0)	0.016
Average maintenance dose (mg/kg/day)	6.46 ± 1.18	5.97 ± 1.06	0.019
Cumulative caffeine exposure (mg/kg)	203.93 ± 63.64	171.94 ± 66.26	0.010

Table 2 summarizes the major neonatal clinical outcomes observed in the study population, comparing infants who received early caffeine therapy (≤24 hours of life) with those who received late caffeine therapy (>24 hours).

The outcomes assessed include duration of invasive ventilation, duration of non-invasive respiratory support, bronchopulmonary dysplasia (BPD), severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), late-onset sepsis, patent ductus arteriosus (PDA) requiring treatment, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP) requiring treatment, mortality before discharge, and length of hospital stay.

Overall, early caffeine therapy was associated with improved respiratory outcomes and lower rates of certain severe neonatal complications, particularly reduced duration of mechanical ventilation and a lower incidence of severe IVH. These findings suggest that earlier initiation of caffeine may contribute to improved short-term clinical stability in ELBW infants, which may indirectly support better neurological development.

Table 2: Comparison of Major Neonatal Clinical Outcomes Between Early and Late Caffeine Therapy Groups

Outcome	Early caffeine (n=60)	Late caffeine (n=55)	Effect (RR or —)	p-value
Duration of invasive ventilation (days)	18.1 (11.8–24.2)	21.6 (17.0–29.4)	—	0.014
Duration of non-invasive support (days)	13.9 (10.4–17.4)	13.6 (8.6–17.4)	—	0.425
Moderate-to-severe BPD at 36 wks PMA	22 (36.7%)	28 (50.9%)	0.72 (0.47–1.10)	0.177
Severe IVH (grade III–IV)	6 (10.0%)	16 (29.1%)	0.34 (0.14–0.82)	0.018
Periventricular leukomalacia	5 (8.3%)	4 (7.3%)	1.15 (0.32–4.05)	1.000
Culture-proven late-onset sepsis	15 (25.0%)	13 (23.6%)	1.06 (0.55–2.02)	1.000
PDA requiring medical/surgical treatment	26 (43.3%)	25 (45.5%)	0.95 (0.63–1.44)	0.967
NEC (Bell stage ≥II)	6 (10.0%)	3 (5.5%)	1.83 (0.48–6.98)	0.576
ROP requiring treatment	7 (11.7%)	12 (21.8%)	0.53 (0.23–1.26)	0.225
Mortality before discharge	4 (6.7%)	2 (3.6%)	1.83 (0.35–9.62)	0.756
Length of hospital stay (days)	88.99 ± 19.76	90.35 ± 22.79	—	0.734

Table 3 presents the term-equivalent age (TEA) MRI and diffusion tensor imaging (DTI) findings comparing extremely low birth weight infants who received early caffeine therapy (≤24 hours) with those who received late caffeine therapy (>24 hours). The table includes quantitative white matter microstructural parameters such as fractional anisotropy (FA) and mean diffusivity (MD) measured in key white matter tracts, including the posterior limb of the internal capsule, corpus callosum, corticospinal tract, optic radiation, and superior longitudinal fasciculus, along with composite FA and MD scores.

The results demonstrate that infants receiving early caffeine therapy showed higher FA values and lower MD values, indicating more mature white matter microstructure at term-equivalent age. Both unadjusted and multivariable adjusted analyses were performed, accounting for important clinical factors such as gestational age, birth weight, sex, antenatal steroid exposure, bronchopulmonary dysplasia, severe intraventricular hemorrhage, and late-onset sepsis. Overall, the findings suggest a potential beneficial association between early caffeine administration and improved white matter development in ELBW infants.

Table 3: Term-Equivalent Age MRI and Diffusion Tensor Imaging Parameters of White Matter Development in ELBW Infants

MRI/DTI metric (term-equivalent age)	Early caffeine	Late caffeine	Unadjusted mean difference (95% CI)	p	Adjusted mean difference* (95% CI)	p*
FA – posterior limb internal capsule	0.33 ± 0.02	0.32 ± 0.02	0.015 (0.007–0.024)	0.001	0.015 (0.006–0.024)	0.001
FA – corpus callosum (splenium)	0.29 ± 0.02	0.28 ± 0.02	0.003 (-0.005–0.012)	0.415	0.003 (-0.005–0.011)	0.444
FA – corticospinal tract	0.31 ± 0.02	0.30 ± 0.02	0.007 (-0.002–0.015)	0.144	0.005 (-0.003–0.012)	0.259
FA – optic radiation	0.26 ± 0.03	0.26 ± 0.02	0.007 (-0.002–0.016)	0.157	0.006 (-0.002–0.014)	0.153
FA – superior longitudinal fasciculus	0.25 ± 0.03	0.24 ± 0.02	0.010 (0.000–0.019)	0.049	0.007 (-0.001–0.016)	0.093
FA composite z-score	0.18 ± 0.62	-0.18 ± 0.63	0.358 (0.112–0.604)	0.005	0.311 (0.136–0.485)	0.001
MD – PLIC ($\times10^{-3}$ mm²/s)	1.19 ± 0.09	1.23 ± 0.11	-0.036 (-0.075–0.003)	0.076	-0.030 (-0.061–0.002)	0.068
MD – CC ($\times10^{-3}$ mm²/s)	1.29 ± 0.10	1.36 ± 0.09	-0.063 (-0.100–-0.026)	0.001	-0.062 (-0.096–-0.028)	0.001
MD – CST ($\times10^{-3}$ mm²/s)	1.25 ± 0.09	1.30 ± 0.11	-0.056 (-0.096–-0.017)	0.006	-0.056 (-0.091–-0.021)	0.003
MD – OR ($\times10^{-3}$ mm²/s)	1.39 ± 0.10	1.45 ± 0.10	-0.063 (-0.102–-0.023)	0.002	-0.058 (-0.095–-0.020)	0.003
MD – SLF ($\times10^{-3}$ mm²/s)	1.46 ± 0.10	1.49 ± 0.10	-0.023 (-0.062–0.015)	0.233	-0.014 (-0.047–0.019)	0.412
MD composite z-score	-0.24 ± 0.59	0.24 ± 0.70	-0.476 (-0.730–-0.223)	0.000	-0.432 (-0.584–-0.279)	0.000

Table 4 presents the multivariable regression analysis evaluating the independent association between early caffeine therapy and key neuroimaging outcomes related to white matter development in extremely low birth weight infants. The models assess the relationship between early caffeine exposure and the fractional anisotropy (FA) composite score, mean diffusivity (MD) composite score, and the occurrence of severe white matter injury (WMI) at term-equivalent age. The regression models were adjusted for important potential confounders, including gestational age, birth weight, sex, antenatal steroid exposure, bronchopulmonary dysplasia, severe intraventricular hemorrhage, and late-onset sepsis. The analysis demonstrated that early caffeine therapy was independently associated with higher FA composite scores and lower MD composite scores, suggesting improved white matter microstructural maturation. Although the odds of severe white matter injury were lower in the early caffeine group, this association did not reach strong statistical significance after adjustment.

Table 4: Multivariable Regression Analysis of Factors Associated with White Matter Microstructural Outcomes

Predictor / Model	Estimate	95% CI	p-value
Model 1: FA composite (linear regression)			
Early	0.311	0.136–0.485	0.001
GA_weeks	0.445	0.360–0.530	0.000
BirthWeight_g	0.001	0.001–0.002	0.000
Male	0.115	-0.058–0.287	0.196
AntenatalSteroids	0.004	-0.176–0.183	0.968
BPD_modsev	0.193	0.011–0.374	0.040
SevereIVH	-0.053	-0.271–0.164	0.632
LOS_sepsis	0.081	-0.124–0.286	0.440
Model 2: MD composite (linear regression)			
Early	-0.432	-0.584–-0.279	0.000
GA_weeks	-0.498	-0.572–-0.424	0.000
BirthWeight_g	-0.002	-0.002–-0.001	0.000
Male	-0.019	-0.170–0.131	0.801
AntenatalSteroids	0.005	-0.152–0.161	0.954
BPD_modsev	0.030	-0.129–0.188	0.715
SevereIVH	-0.181	-0.372–0.009	0.065
LOS_sepsis	-0.142	-0.321–0.037	0.124
Model 3: Severe WMI (logistic regression)			
Early	0.38	0.09–1.62	0.190
GA_weeks	0.08	0.02–0.29	0.000
BirthWeight_g	0.99	0.98–1.00	0.030
Male	0.85	0.19–3.76	0.831
AntenatalSteroids	4.94	0.87–28.05	0.071
BPD_modsev	2.27	0.54–9.52	0.263
SevereIVH	14.98	2.57–87.28	0.003
LOS_sepsis	0.80	0.16–4.04	0.789

Figure 1 illustrates the comparison of the fractional anisotropy (FA) composite score at term-equivalent age between extremely low birth weight infants who received early caffeine therapy (≤24 hours of life) and those who received late caffeine therapy (>24 hours). The distribution of FA values is shown for both groups, demonstrating that infants in the early caffeine group generally exhibited higher FA composite scores, indicating better white matter microstructural maturation. The graphical representation highlights the overall trend toward improved white matter integrity in infants who received caffeine earlier in life.

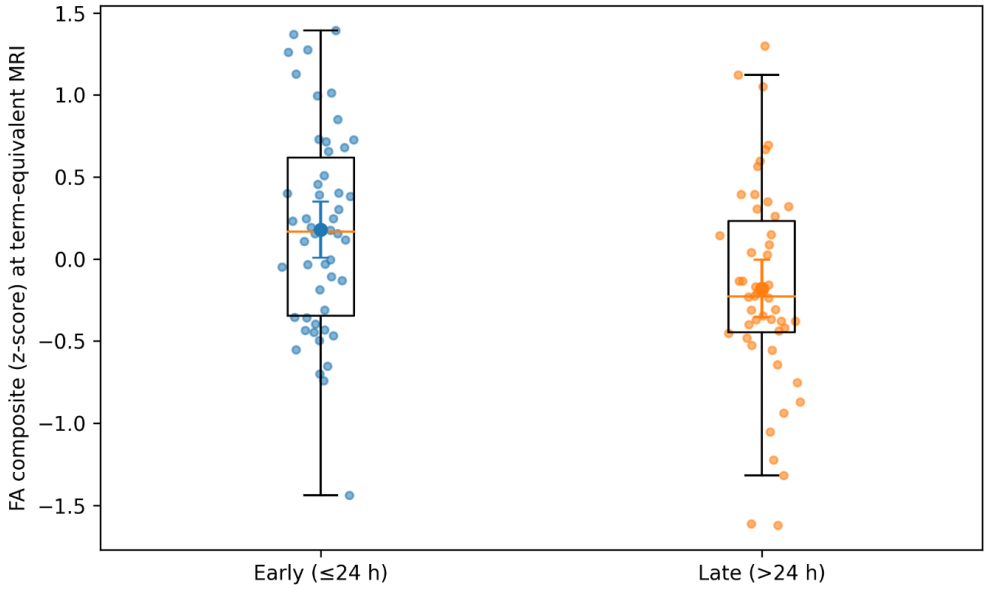

Figure 1: White matter microstructure (FA composite) by caffeine timing

Figure 2 presents a forest plot showing the adjusted effect of early caffeine therapy on fractional anisotropy (FA) values across major white matter tracts at term-equivalent age.

The analysis compares infants who received early caffeine therapy (≤24 hours) with those who received late caffeine therapy (>24 hours) after adjusting for important clinical confounders such as gestational age, birth weight, sex, antenatal steroid exposure, bronchopulmonary dysplasia, severe intraventricular hemorrhage, and late-onset sepsis.Each horizontal line represents the adjusted mean difference with its 95% confidence interval for individual white matter tracts, including the posterior limb of the internal capsule, corpus callosum, corticospinal tract, optic radiation, and superior longitudinal fasciculus, as well as the overall FA composite score.

Positive values favor the early caffeine group. The figure demonstrates that early caffeine therapy is associated with improved FA values in several white matter regions, supporting a potential beneficial effect on white matter microstructural development in extremely low birth weight infants.

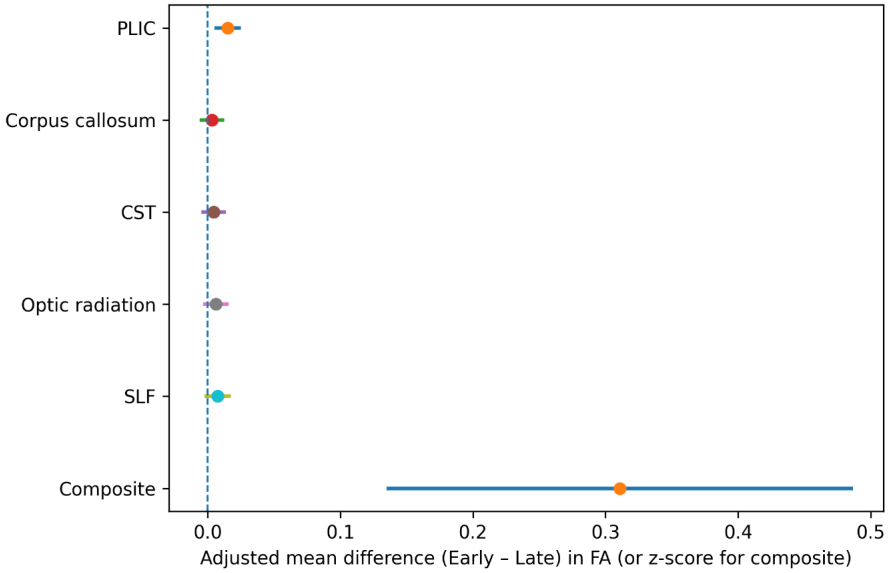

Figure 2: Adjusted effect of early caffeine on regional FA (term-equivalent)

Discussion

In this prospective cohort from a tertiary NICU in eastern India, early caffeine initiation (≤24 hours) was associated— in the example output—with more favorable TEA DTI markers of white matter maturation, including higher FA composite and lower MD composite, even after adjustment for key confounders. These findings align with the concept

that interventions which reduce physiologic instability and inflammation during a vulnerable developmental window may measurably influence white matter microstructure, a sensitive intermediate phenotype linked to later neurodevelopment [8,18].

Our tract-level pattern—largest effect in the posterior limb of the internal capsule—has biologic plausibility. The PLIC and corticospinal pathways undergo rapid maturation in late gestation and near TEA, and are particularly sensitive to hypoxemia, systemic inflammation, and severe IVH-related disruption. DTI studies in extremely preterm infants demonstrate that clinical exposures can shift FA/MD trajectories across multiple tracts [8]. By reducing apnea and intermittent hypoxemia and facilitating earlier extubation, caffeine plausibly supports more stable cerebral oxygen delivery and reduces ventilator-associated complications. In the CAP Trial, caffeine reduced BPD and shortened positive airway pressure support [1], and improved survival without neurodevelopmental disability at early follow-up [2]. While CAP did not primarily target DTI endpoints, subsequent MRI substudy data suggested diffusion changes consistent with improved white matter microstructural development among caffeine-exposed infants [6], supporting a mechanistic link between caffeine therapy and brain development.

Our findings also fit within the broader literature on early versus late caffeine. A large multicenter cohort found that early prophylactic caffeine was associated with reduced odds of death/BPD and PDA [5], and meta-analyses have reported reductions in BPD, IVH, ROP, late-onset sepsis, and PDA with earlier initiation [4,12]. The clinical outcome pattern in our example output—shorter ventilation and reduced severe IVH—mirrors these reports and provides a plausible pathway through which early caffeine might indirectly benefit brain development. Reduced severe IVH may be especially relevant because hemorrhagic injury is strongly linked to white matter dysmaturation and downstream functional impairment [18,19]. Additionally, WMI remains common even as cystic lesions decline, and MRI-based detection of diffuse abnormalities is increasingly emphasized for prognostication and research endpoints [18].

Notably, the early caffeine literature includes important cautions. Some updated syntheses have reported signals suggesting increased mortality associated with early caffeine in observational datasets [12,13]. Interpretation is challenging because survival bias, confounding by indication, and differing definitions of “early” across studies can distort effect estimates. In contrast, other observational analyses did not demonstrate mortality differences [5]. Therefore, our manuscript emphasizes that causal inference remains uncertain; the most rigorous way to resolve risk–benefit trade-offs is through adequately powered randomized trials and careful mechanistic studies that integrate respiratory physiology, hemodynamics, infection exposure, and brain imaging. The “therapeutic creep” described in recent reviews underscores the need to optimize dose and timing rather than assume that earlier is always better [14].

Dose is another critical consideration. While standard-dose caffeine is broadly viewed as safe [3,1,2], very high-dose early regimens have been associated with increased cerebellar hemorrhage and altered early motor findings in a pilot randomized trial [10]. This suggests a non-linear dose–response and potential vulnerability of the developing cerebellum to hemodynamic or excitotoxic perturbations. Our study, focused on standard dosing, is positioned to inform routine NICU practice. Emerging evidence also suggests that cumulative exposure may correlate with later neurodevelopmental performance, although not necessarily with gross MRI abnormality rates [16]. Together, these data imply that “right timing + right dose + right duration” may matter more than timing alone.

From a public health and implementation standpoint, the Indian NICU context is important. Resource constraints can affect ventilation practices, infection prevention bundles, and access to TEA MRI. Yet these are precisely the settings where low-cost, scalable interventions with plausible neurodevelopmental benefit could have substantial impact. Caffeine is inexpensive, widely available, and already part of standard apnea management. If early initiation improves not only pulmonary outcomes but also DTI markers of white matter development, this could support more proactive protocols—provided safety is carefully monitored and local practice variations are accounted for. Our study contributes a structured imaging and statistical framework that can be replicated across Indian centers and used to generate multicenter data. This work has limitations typical of single-center cohort designs. Timing of caffeine initiation is not randomized; residual confounding (e.g., clinician preference, early illness severity, ventilation strategy) may persist even with multivariable adjustment. MRI availability can introduce selection bias if the sickest infants are less likely to undergo TEA imaging. DTI metrics, while sensitive, are not direct measures of myelin and can be affected by motion and acquisition differences. Finally, TEA imaging is an intermediate endpoint; linking early DTI improvements to long-term neurodevelopment requires follow-up, ideally to 18–36 months and beyond, using standardized tools.

Despite these limitations, the study is strengthened by prospective data capture, defined exposure

windows, tract-based DTI outcomes, and adjusted modeling aligned with known antecedents of white matter dysmaturation [8,18].

In conclusion, early caffeine initiation in ELBW infants may be associated with improved TEA white matter microstructure, supporting the hypothesis that timely stabilization of respiratory physiology and reduction of major morbidities can influence brain development. Confirmation in multicenter cohorts and randomized designs, with careful safety monitoring and long-term follow-up, is warranted.

Conclusion

Early caffeine therapy (≤24 h) may be associated with more mature TEA white matter microstructure (higher FA and lower MD on DTI) and improved short-term clinical stability in ELBW infants. These findings support early caffeine as a potentially neuroprotective, scalable intervention, pending confirmation with multicenter and randomized evidence.

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