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VA YECHIMLAR**

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Annotatsiya

Mazkur to'plamda "Yangi davr ilm-fani: inson uchun innovatsion g'oya va yechimlar" mavzusidagi XVIII Respublika ilmiy-amaliy konferensiyasi materiallari jamlangan. Nashrda respublikaning turli oliy ta'lim muassasalari, ilmiy markazlari va amaliyotchi mutaxassislari tomonidan tayyorlangan maqolalar o'rin olgan bo'lib, ular ijtimoiy-gumanitar, tabiiy, texnik va yuridik fanlarning dolzarb muammolari va ularning innovatsion yechimlariga bag'ishlangan.

Ushbu nashr ilmiy izlanuvchilar, oliy ta'lim o'qituvchilari, doktorantlar va soha mutaxassislari uchun foydali qo'llanma bo'lib xizmat qiladi.

Kalit so'zlar: ilmiy-amaliy konferensiya, innovatsion yondashuv, zamonaviy fan, fanlararo integratsiya, ilmiy-tadqiqot, nazariya va amaliyot, ilmiy hamkorlik.

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TIBBIYOT FANLARI

NEONATAL PAIN DURING MEDICAL PROCEDURES AND ITS LONG-TERM EFFECTS ON THE NERVOUS SYSTEM

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Annotation. Advances in neonatal intensive care have markedly improved survival among preterm and critically ill newborns, but survival is accompanied by repeated exposure to invasive, pain-inducing procedures during a period of rapid brain maturation. This narrative review synthesizes clinical and translational evidence on neonatal procedural pain and its long-term consequences for the developing nervous system. Findings indicate that neonates, including extremely preterm infants, possess the neural architecture required to perceive pain while lacking mature descending inhibitory control, leaving them disproportionately vulnerable to noxious stimulation. Cumulative procedural pain exposure in the neonatal intensive care unit (NICU) has been associated with altered brain microstructure, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, blunted or sensitized cortisol reactivity, and later alterations in pain sensitivity, attention, and socio-emotional development. Non-pharmacological interventions such as oral sucrose, non-nutritive sucking, kangaroo care, and breast milk show consistent short-term analgesic benefit, whereas pharmacological approaches carry a more complex risk-benefit profile. The review concludes that systematic pain assessment and multimodal, evidence-based analgesia should be considered standard components of neonatal care, while acknowledging that long-term causal pathways remain incompletely understood.

Keywords: neonatal pain; procedural pain; NICU; neurodevelopment; HPA axis; preterm infants.

NEONATAL DAVRDA TIBBIY MUOLAJALAR VAQTIDA OG'RIQ VA UNING ASAB TIZIMIGA UZOQ MUDDATLI TA'SIRI

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Annotatsiya. Neonatal intensiv terapiya sohasidagi yutuqlar muddatidan oldin tug'ilgan va og'ir ahvoldagi yangi tug'ilgan chaqaloqlarning yashab qolish ko'rsatkichlarini sezilarli darajada yaxshilagan. Biroq yashab qolish ko'pincha miyaning jadal rivojlanish davrida invaziv va og'riq chaqiruvchi tibbiy muolajalarga takroran duch kelish bilan kechadi. Mazkur sharh maqolasida neonatal davrdagi muolajalar bilan bog'liq og'riq hamda uning rivojlanayotgan asab tizimiga uzoq muddatli ta'siri bo'yicha klinik va translatsion tadqiqotlar natijalari umimlashtirilgan. Tadqiqotlar shuni ko'rsatadiki, yangi tug'ilgan chaqaloqlar, jumladan, o'ta muddatidan oldin tug'ilgan chaqaloqlar ham og'riqni sezish uchun zarur bo'lgan nerv tuzilmalariga ega. Biroq ularda og'riqni pastga yo'nalgan tarzda tormozlovchi nerv mexanizmlari hali to'liq shakllanmagan bo'ladi. Shu sababli ular og'riqli ta'sirlarga nisbatan yuqori darajada zaif hisoblanadi. Neonatal intensiv terapiya bo'limida (NICU) muolajalar natijasida to'planib boruvchi og'riqli ta'sirlar miyaning mikrostrukturaviy o'zgarishlari, gipotalamus-gipofiz-buyrak usti bezlari (HPA) o'qi faoliyatining buzilishi, kortizol reaksiyasining susayishi yoki haddan tashqari sezgirlanishi, shuningdek, keyingi hayot davrida og'riq sezuvchanligi, diqqat-e'tibor hamda ijtimoiy-emotsional rivojlanishdagi o'zgarishlar bilan bog'liqligi aniqlangan. Og'riqni kamaytirishga qaratilgan farmakologik bo'lmagan usullar, jumladan, og'iz orqali saxaroza berish, oziqlantirmaydigan emish, «kenguru usuli» (teri-teriga kontakt) va ona suti berish qisqa muddatli analgezik ta'sir bo'yicha izchil ijobiy natijalarni ko'rsatadi. Farmakologik yondashuvlar esa foyda va xavf nisbatini yanada murakkab baholashni talab qiladi. Xulosa qilib aytganda, og'riqni tizimli ravishda baholash hamda multimodal, dalillarga asoslangan og'riqsizlantirish usullaridan foydalanish neonatal tibbiy yordamning standart tarkibiy qismi sifatida qaralishi lozim. Shu bilan birga, neonatal davrdagi og'riqning uzoq muddatli oqibatlariga olib keluvchi sababiy mexanizmlar hali to'liq o'rganilmaganligini ham hisobga olish zarur.

Kalit so'zlar: neonatal og'riq; muolajaga bog'liq og'riq; neonatal intensiv terapiya bo'limi; neyro-rivojlanish; HPA o'qi; muddatidan oldin tug'ilgan chaqaloqlar.

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Introduction. For much of the twentieth century, clinical practice assumed that newborn infants, particularly those born preterm, could not consciously experience pain and therefore did not require analgesia for invasive procedures. This assumption was overturned by a landmark 1987 study demonstrating that neonates who received anesthesia during surgery, rather than paralytic agents alone, had better survival and fewer short-term complications than those left unanesthetized (Anand & Hickey, 1987). It is now well established that the anatomical and neurochemical substrates required for nociception are present from as early as 24 weeks of gestation, even though the descending inhibitory pathways that normally dampen pain signals in older children and adults do not mature until later in development (Vinall & Grunau, 2014).

This developmental mismatch has direct clinical relevance because infants admitted to the neonatal intensive care unit (NICU), especially those born very preterm, are exposed to a striking number of invasive procedures. Estimates suggest that neonates undergo an average of seven to fourteen painful or stressful procedures per day during their NICU stay, with the highest burden occurring during the first days and weeks of life (Ranger & Grunau, 2015; Schiller et al., 2018). Because this period coincides with an exceptionally active phase of synaptogenesis, myelination, and programming of stress-regulatory systems, repeated nociceptive input is increasingly understood not merely as a transient discomfort but as a potential modifier of long-term brain development (Duerden et al., 2018).

Methods. This paper is structured as a narrative literature review rather than a systematic review or original empirical study. Relevant publications were identified through searches of PubMed, PubMed Central, and the Cochrane Library, using combinations of the terms "neonatal pain," "procedural pain," "NICU," "preterm," "neurodevelopment," "cortisol," "HPA axis," and "non-pharmacological analgesia." Priority was given to peer-reviewed systematic reviews, Cochrane reviews, and prospective cohort studies published in English, supplemented by foundational studies frequently cited within this literature (e.g., Anand & Hickey, 1987; Grunau et al., 2005). Reference lists of retrieved reviews were hand-searched for additional primary studies. Given the narrative design, no formal risk-of-bias scoring or meta-analytic pooling was performed; instead, findings are synthesized thematically across the domains of neurophysiology, brain structure, endocrine stress regulation, behavioral outcomes, and clinical management.

Results. Nociceptive circuitry, including peripheral receptors, spinal cord pathways, and thalamocortical projections, is functionally present well before term. However, in preterm infants the excitatory-to-inhibitory balance within the developing central nervous system favors excitation, and descending inhibitory control from the brainstem is immature (Fitzgerald, 2005; Vinall & Grunau, 2014). Consequently, preterm neonates tend to display lower pain thresholds and exaggerated, more generalized responses to noxious stimuli than term infants or older children (Duerden et al., 2018). Specific neuronal populations, particularly subplate neurons and developing oligodendrocytes, appear especially vulnerable to excitotoxicity, oxidative stress, and stress-related inflammation during this window (Ranger & Grunau, 2015). In the immediate term, unrelieved procedural pain has been associated with

physiological instability, including increased intracranial pressure, fluctuations in oxygen saturation, and altered autonomic responses to subsequent painful events (Cong et al., 2024). Repeated exposure without adequate analgesia can also sensitize the nociceptive system, producing exaggerated behavioral and physiological reactions to later, otherwise minor, procedures. A growing body of clinical work links cumulative procedural pain exposure in very preterm infants (born at 24-32 weeks' gestation) to measurable differences in brain development, independent of other prematurity-related risk factors such as illness severity (Ranger & Grunau, 2015). Reported associations include reduced white matter integrity, decreased subcortical gray matter volume, and atypical maturation of the somatosensory cortex (Silva et al., 2026). More recent structural work has also linked greater neonatal pain exposure to smaller amygdala volumes and, in turn, to differences in social-emotional development in children born very preterm (Mueller et al., 2024). These structural findings are broadly consistent with animal models showing that repeated inflammatory or acute pain in the neonatal period increases neuronal apoptosis in regions undergoing active development (Ranger & Grunau, 2015). One of the most consistently studied long-term outcomes is alteration of the HPA axis, the body's principal stress-hormone system. In a cohort of infants born at or below 28 weeks' gestation, higher cumulative neonatal procedural pain exposure predicted a blunted cortisol response and reduced facial reactivity to a later painful stressor at 32 weeks postconceptional age, suggesting an early down-regulation of the HPA axis that was not counteracted by morphine exposure (Grunau et al., 2005).

Discussion. Taken together, the evidence reviewed here supports the view that repeated neonatal procedural pain is not a neutral or purely transient experience but a physiological stressor capable of leaving measurable traces on brain structure, stress-hormone regulation, and later behavior, particularly in infants born very preterm. The consistency of findings across independent domains, structural neuroimaging, HPA-axis reactivity, and behavioral follow-up, strengthens the plausibility of a causal contribution of early pain to later outcomes, even though most human studies remain observational and cannot fully separate the effects of pain exposure from those of prematurity, critical illness, and the therapies used to treat both. The direction of some effects is not uniform. For example, HPA-axis studies have reported both blunted and heightened cortisol reactivity depending on the age at assessment and the nature of the stressor, underscoring that neonatal pain likely reprograms stress systems in a time- and context-dependent manner rather than producing a single, fixed outcome (Grunau et al., 2004, 2005). This complexity has practical implications: it suggests that long-term monitoring, rather than a single follow-up assessment, is needed to characterize the trajectory of stress-system development after NICU discharge. From a clinical standpoint, the asymmetry of risk is instructive. This tension likely explains the persistent variability in analgesic practice across NICUs worldwide.

Several limitations temper these conclusions. Human studies vary widely in how "pain exposure" is quantified (e.g., number of skin-breaking procedures versus composite pain scores), in the confounders they control for, and in the length of follow-up, which complicates direct comparison across cohorts. Emerging tools such as facial-expression-based artificial intelligence and continuous physiological monitoring may eventually improve the objectivity and consistency of pain measurement, but these approaches still require validation in real-world NICU settings before they can be considered a replacement for clinical judgment (Costa

et al., 2025). Future research would benefit from larger, prospective cohorts that track neurodevelopmental outcomes into adolescence, from mechanistic studies clarifying how pain-related stress interacts with genetic and environmental factors, and from trials that directly compare multimodal pain-management protocols on long-term, rather than only procedural, outcomes.

Conclusion

Neonates, including those born extremely preterm, are capable of perceiving pain but lack the mature regulatory systems needed to buffer its effects, making the NICU environment a period of heightened neurodevelopmental vulnerability. Cumulative procedural pain has been linked to altered brain microstructure, dysregulated stress-hormone reactivity, and downstream behavioral and cognitive difficulties, though the underlying causal pathways remain only partially understood. Consistent, validated pain assessment and the routine use of evidence-based non-pharmacological interventions, combined with judicious pharmacological analgesia when clinically warranted, represent the most defensible current approach to minimizing the long-term neurological burden of neonatal medical care.

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