

Review Article

Role of Early Intervention Therapy on long term neuro-developmental outcome of premature newborns

¹Dr. Sudhir D Malwade , ²Dr.Shiji S Chalipat , ³Dr. Geeta R Karambelkar

¹Associate Professor, Department of Pediatrics, Dr D Y Patil Medical College, Dr D Y Patil Vidyapeeth, Pimpri, Pune

²Assistant Professor, Department of Pediatrics, Dr D Y Patil Medical College, Dr D Y Patil Vidyapeeth, Pimpri, Pune

³Professor, Department of Pediatrics, Dr D Y Patil Medical College, Dr D Y Patil Vidyapeeth, Pimpri, Pune

Corresponding author : Dr. Shiji Chalipat

Abstract

Background and objectives: Prematurity is a known precursor to neurodevelopmental disabilities in infants and children. Modern technologies and advances in perinatal care have led to increased survival of extremely premature and low birth weight babies. But despite this, the long-term neuro-developmental impairment in pretermis reported to be 20 -50% and is on the rise. Exposure to abnormal noxious stimuli of NICU environment and prolonged illness could have a deleterious impact on the rapidly developing neonatal brain.

Early intervention programmes are structured programmes offering different sensory and motor stimulations keeping in mind neonatal neuronal plasticity, beginning from NICU environment and continued post discharge. They help in minimizing brain injury and preserve growth. The objectives of the present review were to categorize the key components of early intervention programs for preterm infants and to look for their evidence on long term neurodevelopmental outcome and to suggest feasible protocols for the implementation based on the evidence.

Methods: Detailed literature search was done on research data bases for good quality clinical trials with a robust neurodevelopmental follow up at least till 12 months of age.

Results: There was a tremendous heterogeneity in the intervention provided. Main components of early intervention are – Massage therapy/ Touch stimulation, Music therapy and Visual stimulation.

Conclusion: Early intervention programmes have a positive impact on long-term neurodevelopmental outcome and should be made standard of care across all levels of NICU.

Keywords: massage, neuro-developmental outcome, noise, prematurity, visual stimulation

Introduction:

Environmental experiences and the events that occur in perinatal period can increase developmental vulnerability in premature infants. (1, 2) The in-utero early sensory experiences of the fetus are essential for normal brain development during the perinatal period. Early intervention programs are advocated for newborns to enhance

brain development, taking advantage of their neuronal plasticity. Typically early interventions are more often extended beyond the NICU stay of the neonates and are carried out throughout infancy. They aim at preventing perinatal disabilities, ensuring neuro-protection and providing optimal environmental conditions.

Despite proven benefits, they are not the standard of care in many of the NICUs.

Exposure to unusual sensory stimuli in the Neonatal Intensive Care Units (NICU) can pose risk to the developing brain which can lead to adverse neurodevelopmental outcomes (3). Early stimulation has a decisive impact on the architecture of the brain and directly affects the synaptogenesis and synaptic organization that happens over the course of the child's first three years of life which contributes to the cortical plasticity and a better neuro-developmental outcome. (4, 5) In last three decades, number of trials and systematic reviews has looked in to their effectiveness on short term and long term outcomes. But there is lack of concrete recommendations and tremendous heterogeneity in the interventions provided. Although the evidence for short term benefits is strong, there is paucity of data on long-term neurodevelopmental effects. There are few controversial reports regarding early intervention too (6, 7, 8). Therefore, the objectives of the present review were to assess the key components of early intervention programs for preterm infants and to look for its evidence on long term neuro-developmental outcome, to reinforce the importance of early intervention in clinical practice and to suggest feasible protocols for its implementation.

Methods:

To improve our understanding of effectiveness of early intervention in high risk newborns, we searched the research data bases – PubMed, Google scholar, Cochrane systematic reviews using the search terms – “early intervention, high risk newborns, neuro-development, tactile-kinesthetic stimulation, massage therapy, music therapy, and visual stimulation”. Three independent researchers preselected the articles according to their titles. In

case of doubt, the article was included in the selection process by consensus.

The inclusion criteria:

- Good quality clinical trials on early intervention given in NICU or post discharge or both
- Studies that had a control group that did not receive any intervention other than standard routine care
- Studies that had a robust neurodevelopment follow up at least till 12 months of age
- Articles published in English during last 15 years (2001-2016).

Participants: < 37 weeks of gestation

Interventions: Massage/touch therapy, Music therapy, Visual stimulation and multimodal stimulation

Outcome: Long-term neurodevelopment outcome

Exclusion criteria:

- Those which did not full fill inclusion criteria and
- Studies relating to parent- infant relationship, pain control and acute pain; KMC, swaddling and foreign language papers.

Discussion:

The primary goals of this review were to find out the evidence of early intervention therapy on long-term neurodevelopmental morbidity in premature babies and to stratify the key components.

The literature review on the role of early intervention therapy in premature babies has shown proven short term benefits but evidence for long term benefits are lacking. Many published reports are not recent enough and have limitations on methodology, type and duration of stimulation. There is scarcity of data available focused on current subject from the Indian subcontinent.

To the author’s knowledge this is the only review looking into evidence of long term effects of early intervention on neuro-developmental outcome of premature babies. This review highlights the recent literature search, its implications and suggestions for implementation into clinical practice.

Components of early intervention

- a) Massage therapy / Touch stimulation
- b) Music therapy / Auditory stimulation
- c) Visual stimulation

- a) Massage therapy

Touch is one of the primary sensory systems to develop in utero and is the first language between the parent/ caregiver and the child. It helps in forming a sense of trust and bonding, enhancing communication and understanding cues, promoting self-esteem and acceptance.

A fetus will pull away from an object that touches its face at 8 weeks and by 14 weeks can feel with most part of its body. Massaging, cuddling, rocking, feeding, diapering, are all opportunities for tactile experience for children.

Rationale

The exact mechanism behind tactile stimulation is not clear. Various studies have shown that tactile stimulation can lead to better weight gain (9) (due to insulin and IGF-1 levels, greater gastric activity and less energy expenditure), improved neuro-motor behaviour and stress behaviour (10) which can indirectly help in better neuro-development. There are few animal studies that have shown the positive effect of tactile stimulation over synaptogenesis and organization. (11, 12)

Evidence and Summary of Clinical Trials on Massage therapy

Various studies have shown that tactile stimulation has both short term benefits like better weight gain, reduced stress behaviour, improved / more mature sleep wake cycle, improved neuro behaviour responses and long term benefits like better neurodevelopment especially cognitive domain, body awareness ,improved muscle tone and better weight percentiles (13,14)

The table highlights the summary of studies on touch therapy and the outcome

Author	Type of study	Objectives	Outcome variables	Results
Sandra J Weiss et al, 2004 (15)	RCT Sample size- 108 Mean GA- 30wks	To determine the relationship of early maternal touch to the neurodevelopmental status of low birth weight (LBW) infants.	Neurodevelopmental tests were administered to the infants at age 1 year	Early touch enhances visual motor and gross motor skills at 1 year of age.
Gianni et al, 2006 (16)	RCT Sample size - 36 Mean GA- 27.9wks	To assess the relationship of early maternal touch and neuro-developmental outcome at 36months in VLBW infants	Neurodevelopment assessment at 36 months of chronological age with Griffith’s mental developmental scale and related subscales	Intervention group showed higher scores in personal-social, eye-hand coordination and practical reasoning at 36 months

Procianoy et al., 2010 (17)	RCT Sample size – 73 Mean GA- 30wks	To assess the outcome of Massage therapy started after 48 h of life during hospital stay on growth and neurodevelopment of children at 2 years corrected age.	1) Anthropometry 2) Bayley scales of infant development, second edition (BSID-II). Measured at 2 years of corrected age	Better mental development index (p = 0.035) in intervention group
Abdallah et al., 2013 (18)	RCT Sample size – 66 Mean GA- 32.2wks	To assess the short and long term benefits of Massage therapy given for 10 days on stable newborns	1) PIPP after Massage therapy 2) PIPP at discharge 4) Weight gain 5) Length of stay 6) Breastfeeding duration 7)Cognitive score and Motor score (Bayley scale)	Higher cognitive scores at 12 months corrected age in massage therapy group (p = 0.004)

In a systematic analysis by Benzies et al(19) it was observed that along with babies, mothers were also benefitted in terms of decreased incidence of depression and anxiety symptoms and better psychological bonding with infants.

Indian experience with Massage therapy

For hundreds of years, populations especially in the Indian subcontinent have been routinely applying natural oils to the skin of newborn. Natural oils like coconut oil, safflower oil, mustard oil are preferred than synthetic oils for the massage therapy. Topical oil application has shown to improve skin barrier function, thermoregulation and positive effect on growth. A role for absorption of fats through the thin skin of the preterm has also been suggested. (20, 21)

In studies by Mathai S et al (22)Ho Yb1 et al (23) and Kulkarni et al (24), observed better growth and

development in preterm babies who received tactile stimulation without any adverse effects on physiological parameters with short term benefits. Similar results were also demonstrated by Pepino et al (25) and Field et al (9) in their systematic review on massage therapy.

Summary

Eventhough there was a tremendous heterogeneity among the technique and duration of massage therapy, it is a promising tool which has got beneficial effect on long term neuro developmental outcome.

Music therapy

The structures of the auditory system are formed early in fetal life (20 weeks gestational age).A functional vestibular system forms around 25–29 weeks gestation. Noise, ototoxic medications can cause injury to cochlea and impair the functions of

vestibular system (26). Hair cells can lose their sensitivity to pitch when background sound levels are 60 decibels (dB) or greater. (27)

Sudden or excessive sound can also lead to physiologic instability including changes in heart rate, blood pressure, respiratory rate, oxygen saturation, and inhibit sleep-wake cycles and prevent descent into REM sleep states necessary for maturation and weight gain. (28-33)

The American Academy of Pediatrics (AAP) recommends maximum noise levels of 45db in the NICU. (34,35)But many times these recommendations are not met and sound levels within the NICU vary depending on the design of the unit, time of day, and activity levels in the unit. The sound levels in NICUs range from 51 to 90 dB as reported by various studies. (37-38). In a prospective longitudinal study by Ramesh et al (39) have shown that simple behavioral and environmental modifications which lead to statistically significant reduction in noise levels in NICU.

Long-term effects of noise pollution on children include elevated blood pressures, psychological effects like annoyance / isolation, sleep disturbance and mental health as well as cognitive effects like disturbances in reading, concentration, memory and attention. (40)

Rationale

Music therapy enhances synaptogenesis and synaptic pruning during the early developmental age which is necessary for the normal development of brain. Many cognitive elements of music are processed simultaneously or in sequence by both cerebral hemispheres. Repeated listening and music training stimulates neurological development especially of corpus callosum. (41, 42, 43) Music and language are partners in the brain and awareness to music is critical to language

development in babies.(44)They not only introduce children to words, but help them learn rhythm, sequences, spatial and math skills.(45)

Evidence for Music therapy

A meta-analysis on music therapy by Standley et al (46) and systematic review by Vander Heijden et al (47), have shown a significant short term benefits like, slowing of heart rate and respiratory rate, improve sucking behavior, aid in sleep and promote states of quiet alertness which might be conducive for the brain development later on. The researchers have used different modalities for music therapy; for example, live music which included active singing by mother or certified music therapist - lullabies or nursery rhymes, live instrumental music – guitar, harp or drum, gatobox, ocean disc and Recorded music which included recorded lullabies, pacifier activated lullabies, instrumental music –Mozart music, classical music etc.

At present there are not many studies showing evidence for long term neuro-developmental effect of music on NICU graduates. Only study which showed effect on neurodevelopment was done by Nocker et al, (48) exposing premature babies to a recording of baby's own mother's voice in the hospital, that demonstrated better verbal and motor development at the age of 5 months which persisted up to 20 months of age along with better verbal skills at the age of 6 years.

Schwartz et al and Standley et al (49, 50) had shown that along with physiological responses, there was significant difference in average daily head growth across time in premature infants exposed to lullabies. A better head circumference is a reliable indicator of brain development.

Summary

The evidence suggests the consideration of inclusion of music therapy protocols in best

practice standards for preterm babies in NICU. Benefits were greatest for live music therapy (MT) and for use early in the infant's NICU stay. There is a need for implementation of noise reduction protocols as a standard of care in NICU.

Implications for clinical practice

- **Environmental modifications (39)**
 - o Decreasing the ambient noise levels in the NICU in the permissible range of 45-50 dB as per AAP guidelines by installing a decibel meter in NICU
 - o Volume of alarms and phone ringtones should be tuned down to 45-50 dB
 - o Avoiding discussions during rounds and shouting across distances
 - o Staff awareness on deleterious effects of noise
- **Music therapy**
 - o Simple procedure - can be administered by staff nurses in NICUs and mothers/caretakers at home
 - o Can be incorporated into daily clinical practice
 - o Non invasive
 - o Cost effective

Visual Stimulation

The visual system is the last among all the sensory modalities to develop which matures only around 39 to 40 weeks. Visual experience for healthy visual development requires ambient light and not direct light. AAP guidelines recommend an illumination of 650 lux (luminous intensity) for observation and 2000 lux for procedures (51). Most NICUs have bright lights throughout day and night. Spot lights for procedures and phototherapy units provide

much higher illumination. Continuous high light exposure to preterm infants causes retinal damage, disturbance of sleep patterns, disturbed development of circadian rhythm and poor growth.

Physiology and Rationale

Circadian clock in human fetus is established at around 25 weeks of gestational age. Exposure to rhythmic/cycled low level ambient light, prevention of eyes from direct light exposure and facilitation of sleep cycle for development of circadian rhythm in preterm would in turn help in later brain development. (52)

Visual cortex is ready to accept environmental stimuli right after birth. Visual stimulation can modify and stabilize synaptic connection in visual cortex. (53) Mature visual preference, visual orientation pattern and visual fixation are demonstrated at 32 weeks of gestation, but fully mature by 34-35 weeks. Developmental process that precedes the onset of binocular vision can be programmed with repeated exposure to visual stimuli. Early visual stimulation can stimulate the development of smooth pursuit which matures between 2-6 months of age. (54). Visual preferences include patterned surfaces over plain surfaces, curvilinear over straight contour, contrast images and large patterned elements.

Evidence for visual stimulation

A meta-analysis on cycled lighting effects on preterm infants in NICU reported a trend towards improved weight gain, shorter length of hospital stay and less incidence of Retinopathy of Prematurity (ROP) when compared to near darkness or continuous bright light [52]. In another study by Lasky et al, infants who were exposed to diurnally-cycled lighting while in intensive care experienced both physical and behavioral developmental benefits; improved weight gain,

early transition to oral feeding and shorter hospital stay [51].

In a study by Rosenblith JF et al (55) it was observed that those children who had a poor performance or low scores on visual fixation and following had affected gross motor performance at 4 years of age.

Dubowitz et al (56) described, that for visual stimulation newborn should be kept propped up to 30° supine position, with ambient back ground light and stimulus should be given 18 cm (7inches) from eyes for optimal response. Black and white target, checker board, skein of red wool can be used as visual stimuli. Infant's ability to attend any length of time may be limited by gestational age, behavioral state and effects of medical condition.

(57)

Summary and implications for clinical practice

Thus the visual care interventions for preterm infants can be started around 32-34 weeks of gestation. It includes exposure to rhythmic low level ambient lights for entrainment of circadian rhythm, prevention of eyes from direct light exposure, and facilitation of sleep cycles along with visual stimulation using black and white target, checker board, skein of red wool.

Multimodal stimulation

Multimodal stimulation means combination of two or more interventions or one intervention with parent education/intervention. The following is summary of various studies based on multimodal stimulation.

	Author	Type of study	Intervention	Outcome variables	Conclusion
1	Nelson et al, 2001(58)	Randomized controlled trial Sample size – 37	Multisensory stimulation (auditory, tactile, visual and vestibular) done in infants with severe CNS injury Twice daily for 5days a week, starting in NICU and continued till 2 months of corrected age	BSID II at 12 months	Better motor and mental performance and had 23% fewer cerebral palsy diagnosis at 1 year
2	Ohgi et al, 2004(59)	RCT Sample size – 24	Intervention group received a Neonatal Behavioral Assessment scale (NBAS)-based intervention combined with developmental support Intervention started in NICU till 6 months of corrected age	BSID II at 6 months	BSID score was higher in intervention group compared to control group
3	MKC	RCT	CDC model of early stimulation	BSID II at 1	Statistically

	Nair et al, 2009 (60)	Sample size -800	started in NICU and continued till 2 years of age	year and 2 years	significant higher score for MDI and PDI at one and two year of age in the intervention group
4	Koldewijn et al 2009(61)	Multicenter RCT Sample size - 176	'Infant Behavioural Assessment and Intervention Program' (IBAIP) vs standard follow-up. Intervention group received 1-hour sessions, with the first session just before discharge, followed by 6 to 8 home visits up to 6 months' corrected age.	Dutch version BSID-II at 6 months	Improved motor and cognitive outcome at 6 months.
5	Teti et al, 2009 (62)	RCT Sample size -173	Intervention consisted of psychoeducational components and a parent-administered infant tactile stimulation commenced before discharge from hospital and continued until 4 months' corrected age.	BSID II at 4 months	Better MDI scores among intervention group
6	Wu et al, 2014 (63)	RCT Sample size -211	Randomized controlled trial with 3 arms, comparing a clinic-based intervention programme (CBIP), a home-based intervention programme (HBIP) and a usual care program from shortly after birth until 12 months' corrected age.	BSID III at 24 months	Better motor, cognitive and behavioral outcome in intervention group

In the Cochrane Database of Systematic Reviews 2015 by Spittle A, (64), the meta-analysis concluded early intervention programmes for preterm infants have a positive influence on cognitive and motor outcomes during infancy, with the cognitive benefits persisting into pre-school age.

A prospective, randomized controlled trial by N.Meena et al (65) providing early physiotherapy in premature infants showed better neurodevelopmental outcome at 6 months of corrected age. Similar results were reported by Gianní ML et al (66), Spittle et al (64) and Yamashita Y1et al (67) showing all interventions

having positive effect on child's neuro-development at 2 and 3 years of life.

Proposed guidelines for clinical practice based on literature review

	Tactile stimulation	Music therapy	Visual stimulation
Delivery method and content	Moderate pressure massage from head to toe and proximal to distal preferably using coconut oil	Recorded lullabies/devotional hymns in the desired range (30-65 db)	Checker board, target pattern, skein of red wool
Who will deliver the sessions	Trained staff nurse/ caretaker preferably mother after discharge	Trained staff nurse/ Parent or Caretaker after discharge	Trained staff nurse/ caretaker preferably mother after discharge
When to start the sessions	Immediately after admission to NICU/once hemodynamically stable	Immediately after admission to NICU	32-34 weeks hemodynamically stable neonate
How to give Sessions	15 minutes, twice a day	Through snugly fitting head phones for 15 minutes, twice a day	5-10 minutes twice a day during feeding or wake cycles with baby 30 degree supine and low background lighting, stimulus at a distance of 18cm.
Other specifications		The ambient noise level in the NICU would be ensured and kept between 30-65 db measured with the help of a decibel meter. Staff sensitization about harmful effects of loud noise on neonates should be done	The ambient light in NICU would kept below 650 lux for observation and below 2000 lux for procedures which should be monitored by Lux meter. Babies should be exposed to diurnal cycle lighting to establish circadian rhythms

Conclusion

There is tremendous heterogeneity in Early Intervention Programme (EIP) for premature babies provided in NICU and post discharge period. These programmes have definitive short term benefits and few of the interventions also have a positive impact

on longtermneuro-developmental outcome that may persist till early school age. With increasing number of Neonatal Intensive Care Units that aim at survival without impairment, early development interventions and environmental modifications in

NICU should be made a standard of care. Family centered developmentally supportive care should be encouraged. It is essential to sensitize NICU staff, doctors and parents regarding cost effective implementation of early intervention and their benefits. Rigorous randomized controlled trials aiming at long term neuro developmental outcome along with homogeneity in providing early

developmental interventions are needed to put research into clinical practice. With high burden of neonatal mortality and lack of infrastructure towards developmentally oriented care, this review might help the policy makers to evolve better programmes and to frame guidelines for early developmental care for existing and budding NICUs in developing world.

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