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Primeira recomendação brasileira de fisioterapia para estimulação sensório-motora de recém-nascidos e lactentes em unidade de terapia intensiva

First Brazilian recommendation on physiotherapy with sensory motor stimulation in newborns and infants in the intensive care unit

RESUMO

Objetivo: Apresentar as diretrizes de estimulação sensório-motora para recém-nascidos e lactentes em unidade de terapia intensiva., **Métodos:** Trata-se de um método de delineamento misto com revisão sistemática da literatura e recomendações com base na evidência científica e opiniões de fisioterapeutas especialistas em fisioterapia neonatal de estudos publicados entre 2010 e 2018 nas bases de dados MEDLINE® e Cochrane, que incluiu recém-nascidos (pré-termo e a termo) e lactentes (entre 28 dias e 6 meses de idade) admitidos à unidade de terapia intensiva e submetidos a métodos de estimulação sensório-motora. Os estudos encontrados foram classificados segundo o escore GRADE por cinco fisioterapeutas em diferentes regiões do país e apresentados em oito congressos científicos para discussão das diretrizes de práticas clínicas., **Resultados:** Foram incluídos 89 artigos para construir as diretrizes de práticas clínicas. Estimulação auditiva, gustatória e contato pele a pele se destacaram por melhorar os sinais vitais, e a massagem terapêutica, assim como a estimulação multimodal tátil-cinestésica por melhorar o peso ou a sucção., **Conclusão:** Embora todas a modalidades tenham boas avaliações para controle da dor ou do estresse, é recomendado que os procedimentos de estimulação sensório-motora sejam adaptados às necessidades específicas da criança, e as intervenções sejam realizadas por profissionais experientes.

Descritores: Lactente; Recém-nascido; Estimulação sensório-motora; Desenvolvimento neuropsicomotor; Desenvolvimento infantil; Desempenho psicomotor; Unidades de terapia intensiva, neonatal

INTRODUÇÃO

A estimulação sensório-motora (ESM) para recém-nascidos (pré-termo e a termo) e lactentes na unidade de terapia intensiva (UTI) é uma intervenção precoce que inclui uma série de estratégias com o objetivo de melhorar o desenvolvimento neuropsicomotor (DNPM) pela promoção de estímulos sensoriais e com base no nível de desenvolvimento funcional, na idade gestacional (IG) ao nascer e no peso dessa população.[1]

O objetivo primário da ESM é organizar os sistemas do corpo humano, como tátil, cinestésico, vestibular, olfatório, paladar, auditivo, visual e/ou uma combinação deles.[1] Na UTI, os recém-nascidos e lactentes frequentemente apresentam condições clínicas moderada ou altamente complexas, que podem levar à instabilidade dos sistemas neurológico, hemodinâmico e cardiorrespiratório, demandando conhecimento técnico e científico para a condução das avaliações gerais dos candidatos à ESM.[2,3]

Conflitos de interesse: Nenhum.

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Apesar dos avanços tecnológicos e esforços multiprofissionais, recém-nascidos extremamente prematuros (IG < 28 semanas) e com peso extremamente baixo (< 1.000g) continuam em alto risco de óbito e incapacidade funcional (em curto, médio e longo prazo). Cerca de 20% a 50% dos sobreviventes têm risco de morbidade, inclusive alterações do crescimento pôndero-estatural e DNPM.[2]

A ESM facilita o DNPM típico e previne ou minimiza os efeitos danosos do ambiente da UTI e suas intervenções no crescimento pôndero-estatural. Assim, pode ser aplicada para tratar alterações do DNPM resultantes da prematuridade, doenças e/ou alterações/complicações nos períodos pré-natal, perinatal ou intranatal e após o parto.[4-6]

O objetivo do presente estudo é apresentar diretrizes para a prática clínica relativas à ESM em recém-nascidos e lactentes na UTI.

MÉTODOS

Delineamento do estudo

Estudo com delineamento misto desenvolvido de acordo com os quatro estágios descritos a seguir.

Estágio 1 – submetido para aprovação da criação deste documento e a classificação da ESM, como segue:

Recomendação: os achados principais se baseiam em pelo menos um ensaio clínico, considerando a evidência científica de benefícios *versus* riscos para recém-nascidos e lactentes internados na UTI, viabilidade de comparações com outras opções terapêuticas e confirmação da confiabilidade da evidência apresentada para dar suporte ao uso ou rejeição da ESM na prática clínica dos fisioterapeutas.

Perguntas de orientação: são considerados os domínios PICO, ou seja, P para paciente (*patient*; recém-nascido ou lactente); I para intervenção (*intervention*; qualquer intervenção de ESM); C para comparação (*comparison*; comparação transversal ou longitudinal, controle com intervenção ou placebo, ou outra intervenção de ESM) e O para desfecho (*outcome*; estudos com inclusão de desfechos pôndero-estaturais e seus índices; melhora da qualidade do sono; redução da dor; aumento de qualquer domínio do DNPM; outros desfechos relacionados ao DNPM – exemplo: circunferência do braço, crescimento ósseo – e crescimento pôndero-estatural).

Estágio 2 – foi realizada uma busca sistemática nas bases de dados MEDLINE® e Cochrane quanto a estudos sobre ESM publicados entre 2010 e 2018. Os descritores utilizados incluíram indexadores controlados contidos em *Health Sciences Descriptors* (DeCS, disponível em http://decs.bvs.br/P/decsweb2014.htm) e/ou em *Medical Subject Headings* (MeSH, disponível em http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh). Utilizou-se também uma série de termos livres relacionados a cada modalidade de ESM (vide cada subitem das Recomendações em "descritores"). Os termos de pesquisa foram combinados utilizando operadores booleano "OU" e "E", bem como suas palavras correspondentes em inglês. Cinco especialistas conduziram a pesquisa sistemática e avaliaram os estudos de forma independente, segundo cada modalidade de ESM. As discordâncias foram resolvidas por consenso entre todos os presentes nas discussões presenciais e/ou via *Skype*. Os especialistas foram subdivididos em pares para redigir um relato a respeito das intervenções de ESM. Todos os especialistas eram fisioterapeutas com experiência maior ou igual a 12 anos em intervenções de ESM em pacientes recém-nascidos e lactentes (até 6 meses de idade) na UTI.

Estágio 3 – os dados parciais foram apresentados ao público em diferentes congressos de pediatria e neonatologia, quando os participantes puderam dar suas opiniões e oferecer sugestões e comentários. Os cinco especialistas analisaram as sugestões e os comentários fornecidos pelo público nos eventos e fizeram alterações pertinentes no documento.

Estágio 4 – criação e redação do documento, segundo as três modalidades de ESM (estimulação unimodal e multimodal e exercícios/mobilizações) e os tipos de intervenção encontrados na literatura (Figura 1).

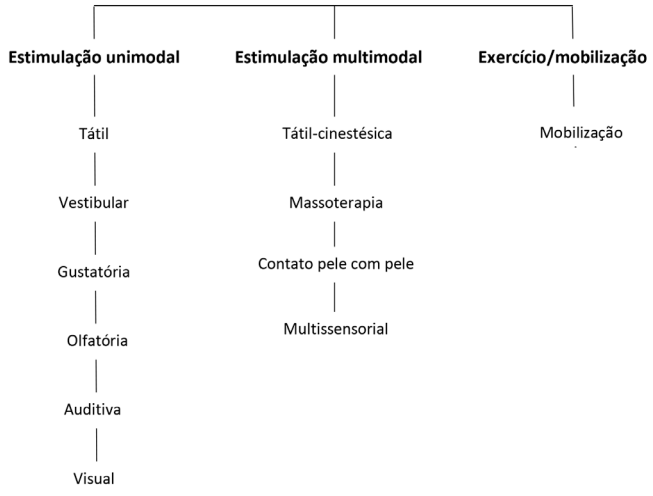

Figura 1 - Recomendações sobre a modalidade de estimulação sensório-motora para recém-nascidos e lactentes internados na unidade de terapia intensiva neonatal.

Critérios de inclusão e exclusão

Foram incluídos os ensaios clínicos que cumpriam os seguintes critérios: (1) estudo clínico controlado ou não,

comparativo ou não, randomizado ou não, ou cruzado; (2) o estudo incluía algum tipo de intervenção de ESM; (3) população do estudo constituída de recém-nascidos e/ou lactentes e (4) UTI neonatal como local do estudo. Artigos duplicados e estudos de revisão, relatos de caso, editoriais e cartas ao editor foram excluídos, porém, quando considerados relevantes, foram incluídos na introdução e/ou comentários do documento.

Avaliação da qualidade

Os estudos identificados foram classificados segundo o escore *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) modificado.[7] O GRADE é um sistema de classificação de evidências com uma escala de quatro pontos (alta, moderada, baixa e muito baixa). Os ensaios randomizados começam com escore 4/4 (alta) e podem ser rebaixados com base em falhas metodológicas. Quando não havia literatura publicada disponível, utilizamos a opinião de fisioterapeutas especializados. As avaliações segundo o GRADE são apresentadas na tabela 1, sendo os indicadores clínicos apresentados por sinais + indicando o grau de certeza científica: + para recomendação muito fraca, ++ para fraca; +++ para moderada e ++++ para forte.

RESULTADOS

Incluíram-se 89 artigos. Os dados parciais foram apresentados em diferentes congressos de pediatria e neonatologia: Congresso Brasileiro de Medicina Intensiva - AMIB (CBMI-AMIB) em Florianópolis (SC), em 2014; Simpósio Internacional de Fisioterapia Cardiorrespiratória em Salvador (BA), em 2014; CBMI-AMIB em Goiânia (GO), em 2014; CBMI-AMIB na Costa do Sauípe (BA), em 2015; CBMI-AMIB em Porto Alegre (RS), em 2016; CBMI-AMIB em Natal (RN), em 2017; Congresso Panamericano de Terapia Intensiva, no Rio de Janeiro (RJ) em 2017; CBMI-AMIB São Paulo (SP), 2018 e CBMI-AMIB em Fortaleza (CE), em 2018, com a participação de cerca de 600 fisioterapeutas atuantes na área de terapia intensiva neonatal e pediátrica oriundos de diferentes regiões do Brasil.

Os indicadores clínicos classificados pelo sistema GRADE são apresentados na tabela 1. As tabelas 1 a 9, no apêndice 1, mostram um resumo dos dados para os estudos incluídos.

DISCUSSÃO

Estimulação unimodal

A estimulação unimodal inclui intervenções de ESM que fornecem apenas um tipo de estimulação sensorial a recém-nascidos e lactentes, em conformidade com a hierarquia do desenvolvimento fisiológico dos subsistemas sensoriais como tátil→vestibular→paladar→olfatório→auditivo→visual.[6]

Estimulação tátil

Recomendação: a estimulação tátil é recomendada para reduzir o estresse, avaliado pelos níveis urinários de cortisol e aplicada pela utilização da intervenção de toque humano

Tabela 1 - Classificação dos indicadores clínicos, certeza científica e recomendações para estimulação sensório-motora

Indicadores clínicos	Tátil	Auditivo	Olfatório	Gustatório	Tátil-cinestésico*	Massagem*	Pele com pele*	Multissensorial*	Mobilizações*
Reduz a dor/estresse ou melhora a organização comportamental	+++	+++	+++	++++	+++	++++	++++	++++	
Melhora os eventos fisiológicos vitais (regula FR, FC, SpO_2, temperatura e reduz episódios de apneia)	++	++++	+++				++++		
Melhora os ciclos de sono-vigília	++	+			++	+			
Acelera a maturação cerebral					+	+		+++	
Melhora o peso ou a sucção ou promove progressão mais rápida para alimentação oral total		++			+++	+++	++++	+++	
Melhora a massa óssea ou a força muscular ou a maturação do tônus muscular					+++			+++	+++
Diminui o tempo de hospitalização ou reduz o número de morbidades		++			+++	+++	++++		

FR - frequência respiratória; FC - frequência cardíaca; SpO_2 - saturação sanguínea de oxigênio. Grau de certeza científica: ++++, forte; +++, moderado; ++, fraco; +, muito fraco. * Estimulação multimodal: intervenções de estimulação sensório-motora que combinam dois ou mais tipos de estímulos sensoriais.

suave (THS);[8] reduz a intensidade da dor, conforme avaliação pela *Neonatal Infant Pain Scale* (NIPS); altera a frequência cardíaca (FC) e a respiratória (FR) associadas com estímulos dolorosos, pelo uso da intervenção de toque terapêutico (TT)[9] e melhora o sono, conforme avaliação pela *Anderson Behavioral State Scale* (ABSS) após a intervenção com THS e o protocolo de Yakson.[10] Os indicadores clínicos classificados segundo sistema GRADE são apresentados na tabela 1.

Estimulação vestibular

Recomendação: alguns métodos de posicionamento funcional, que podem também ser utilizados para estimulação vestibular (por exemplo: redes, frequentemente utilizadas em UTIs brasileiras), não apresentaram o grau de evidência científica necessária para inclusão em estimulação unimodal e, portanto, foram incluídos entre os métodos de ESM multimodal.

Estimulação auditiva

Recomendação: a estimulação auditiva é recomendada para aumentar a saturação de oxigênio (SpO_2) e reduzir a FC por meio da exposição a canções de ninar cantadas pelos pais;[11] aumentar a SpO_2 por meio de exposição a canções de ninar de Brahms ou alguma cantada/gravada pela mãe;[12] diminuir as respostas fisiológicas de FC e comportamentais (estado de sono-vigília e expressões faciais de dor) durante e após estímulo doloroso;[13,14] reduzir o dispêndio energético em repouso por exposição a músicas de Mozart (efeito Mozart);[15] diminuir a FC e a FR por exposição a canções de ninar e redução da FC durante exposição a músicas de Mozart;[16] reduzir a FC e a FR pelo uso de três tipos de intervenção (canções de ninar, sons semelhantes aos batimentos cardíacos e sons imitando a respiração); melhorar o comportamento de sucção com sons semelhantes a batimentos cardíacos, aumentar a ingestão calórica e melhorar o comportamento de alimentação (taxa de sucções por minuto) com utilização de canções de ninar;[17] diminuir a frequência de eventos adversos cardiorrespiratórios[18] (definidos como ocorrência de apneia superior a 20 segundos e/ou diminuição na FC abaixo de 100bpm para bebês com IG inferior a 34 semanas ou abaixo de 80bmp para lactentes com IG acima de 34 semanas) com ciclo de sono-vigília ruim[19] e choro;[20] diminuir o pico de FC durante alimentação, melhorar a sucção, promover a transição mais rápida para alimentação oral e diminuir o tempo de hospitalização.[21] Um estudo não encontrou efeitos benéficos fisiológicos e comportamentais das canções de ninar para lactentes prematuros. Os autores não encontraram diferenças significantes entre a intervenção (canções de ninar), placebo e grupos controle em termos de respostas fisiológicas e comportamentais.[22] Os indicadores clínicos classificados segundo sistema GRADE são apresentados na tabela 1.

Estimulação olfatória

Recomendação: a estimulação olfatória é recomendada para prevenir apneia com uso de estimulação com fragrância de baunilha[23] e reduzir a dor com utilização do odor de leite materno.[24] A estimulação olfatória não é recomendada para diminuir o gasto energetico em repouso com utilização de fragrância de baunilha,[25] e um odor não familiar (baunilha) teve efeito calmante observável em recém-nascidos a termos submetidos a procedimento doloroso.[26] Os indicadores clínicos classificados segundo sistema GRADE são apresentados na tabela 1.

Estimulação gustatória

Recomendação: estimulação gustatória com uso de saturação sensorial,[27] leite materno,[28] sucção assistida,[29,30] e soluções doces (glicose, sucralose e dextrose) são recomendadas para diminuição da dor.[31-35] Quando se compararam estímulos com soluções doces (glicose, sucralose e dextrose) e com placebo,[33-45] as primeiras apresentaram diminuição da dor; apenas um estudo comparou a sucralose oral e creme EMLA®,[37] e a combinação de sucralose com creme EMLA® teve efeito analgésico maior. Os indicadores clínicos classificados segundo sistema GRADE são apresentados na tabela 1.

Estimulação visual

Recomendação: a estimulação visual foi incluída na ESM multimodal em razão da ausência de evidência científica que cumprisse os critérios de inclusão dessas recomendações na estimulação unimodal.

Estimulação multimodal

A estimulação multimodal inclui intervenções de ESM que combinam dois ou mais tipos de estímulo sensorial, como estimulação tátil-cinestésica, massagem terapêutica, controle pele a pele e estimulação multissensorial (Figura 1).

Estimulação tátil-cinestésica

Recomendação: a estimulação tátil-cinestésica é recomendada para melhorar o ganho de peso e reduzir o tempo de hospitalização,[46] aumentar a atividade parassimpática durante o sono,[47,48] melhorar a força muscular e mineralização óssea,[49] otimizar o desempenho do comportamento motor,[50] baixar os níveis de bilirrubina,[51]

favorecer a maturação da atividade elétrica cerebral,[52] favorecer padrões motores mais maduros e comportamentos mais regulados e organizados,[53] melhorar o componente motor e encurtar o tempo de hospitalização,[54] melhorar a deposição de gordura em recém-nascidos pré-termo[55] e contribuir para fortalecimento do sistema imunológico e ganho de peso.[56,57] Os indicadores clínicos classificados segundo sistema GRADE são apresentados na tabela 1.

Massagem terapêutica

Recomendação: a ESM utilizando massagem terapêutica é recomendada para melhorar o ganho de peso,[58-60] aumentar a frequência de episódios de defecação,[61,62] diminuir os níveis transcutâneos de bilirrubina,[61-63] reduzir os escores de dor[64] e aumentar o estado de alerta após a massagem.[65] Os indicadores clínicos classificados segundo sistema GRADE são apresentados na tabela 1.

Contato pele a pele

Recomendação: a ESM com utilização de contato pele a pele é recomendada para recém-nascidos sob ventilação mecânica,[66-70] reduz a dor durante procedimentos dolorosos,[71-77] alivia o estresse,[78,79] controla a temperatura corpórea,[80] associa-se com menores níveis salivares de cortisol em recém-nascidos,[79] melhora a eficácia da amamentação no seio ou ganho de peso[81-85] e diminui a custo da internação.[86]

Um estudo[84] não demonstrou uma diminuição nos níveis salivares de cortisol em recém-nascidos pré-termo; outras investigações[85,86] não produziram evidência significante em termos de ganho médio diário de peso. Os indicadores clínicos classificados segundo sistema GRADE são apresentados na tabela 1.

Estimulação multissensorial

A estimulação multissensorial combina diferentes tipos de estímulos que não precisam, necessariamente, ser oferecidos ao mesmo tempo. Seus benefícios dependem da maturidade do sistema nervoso central e dos subsistemas sensoriais de recém-nascidos.[4,87,88]

Recomendação: a estimulação multissensorial é recomendada para melhorar o escore neuromotor e a maturação do tônus muscular em recém-nascidos pré-termo pela aplicação do protocolo de "estímulo auditório, tátil, visual e vestibular – ATVV", melhora a organização comportamental, eleva a frequência de comportamentos orais, aumenta o tempo em estado de alerta,[89,90] melhora a interação materno-infantil com ATVV[91] e aumenta o ganho pôndero-estatural.[92] Os indicadores clínicos classificados segundo sistema GRADE são apresentados na tabela 1.

Exercícios/mobilização

Os exercícios/mobilização (passiva ou ativa assistida) podem ser iniciados para recém-nascidos pré-termo clinicamente estáveis com elevado risco de doença osteometabólica e IG inferior a 32 semanas e/ou peso ao nascer inferior a 1.000g.[93,94] O protocolo de Moyer-Mileur[93] foi utilizado em todos os estudos que cumpriram os critérios de inclusão dessas recomendações.

Recomendação: a ESM com utilização de mobilizações realizadas por fisioterapeutas é recomendada para aumentar peso, estatura e comprimento tibial,[95] elevar a velocidade de propagação de ultrassom na tíbia,[95,96] ampliar a circunferência do braço,[97] aumentar os marcadores de formação óssea e diminuir os marcadores de reabsorção óssea.[98,99] Os indicadores clínicos classificados segundo o sistema GRADE são apresentados na tabela 1.

CONCLUSÃO

A única modalidade de estimulação sensório-motora com elevado grau de certeza científica foi a estimulação pele a pele, seguida por estimulação multissensorial. Todas as modalidades tiveram boas classificações para controle da dor ou do estresse. A estimulação auditiva se destaca por melhorar os sinais vitais, e a massagem terapêutica, estimulação tátil-cinestésica e estimulação multissensorial por melhorar o peso ou a sucção. Recomenda-se que os procedimentos de estimulação sensório-motora sejam adaptados às necessidades específicas da criança, e as intervenções sejam realizadas por profissionais experientes.

CONTRIBUIÇÃO DOS AUTORES

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DISPONIBILIDADE DOS DADOS E MATERIAIS

O conjunto de dados utilizado e analisado durante o presente estudo está disponível por solicitação razoável ao autor correspondente.

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ABSTRACT

Objective: To present guidelines on sensory motor stimulation for newborns and infants in the intensive care unit.

Methods: We employed a mixed methods design with a systematic review of the literature and recommendations based on scientific evidence and the opinions of physiotherapists with neonatal expertise. The research included studies published between 2010 and 2018 in the MEDLINE® and Cochrane databases that included newborns (preterm and term) and infants (between 28 days and 6 months of age) hospitalized in the intensive care unit and submitted to sensory motor stimulation methods. The studies found were classified according to the GRADE score by five physiotherapists in different regions of Brazil and presented at eight Scientific Congresses held to discuss the clinical practice guidelines.

Results: We included 89 articles to construct the clinical practice guidelines. Auditory, gustatory and skin-to-skin stimulation stand out for enhancing vital signs, and tactile-kinesthetic massage and multisensory stimulation stand out for improving weight or sucking.

Conclusion: Although all modalities have good ratings for pain or stress control, it is recommended that sensory motor stimulation procedures be tailored to the infant's specific needs and that interventions and be carried out by expert professionals.

Keywords: Infant; Infant, newborn; Sensory motor stimulation; Neuropsychomotor development; Child development; Psychomotor performance; Intensive care units, neonatal

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APÊNDICE 1

Table 1S - Studies included for unimodal tactile stimulation recommendations

Author	Type of study	Sample	Interventions	Main outcomes	Main results
Asadollahi *et al.*[8]	*Randomized controlled trial*	*n = 78 NB, GA: 30 - 36 weeks, Weight: 1,000g - 1,800g, Without ventilatory support*	*Tactile stimulation performed 7 to 10 days after birth; interventions conducted 3 times a day for 5 consecutive days, Randomized into 3 groups:, Control Group, n = 24: the physiotherapist placed the palm of one hand on the NB's forehead for 15 minutes (fingers on the eyebrows) and the other on the lower abdomen to support the spine and hip , Gentle Human Touch Group, n = 27 , Massage Group, n = 27*	*The decrease in stress assessed by urine cortisol level*	*A decline in cortisol level in the Gentle Human Touch and Massage Group, but significantly higher in the latter*
Ramada *et al.*[9]	*Prospective controlled trial*	*n = 40 NB (21 preterm NB and 19 term NB), GA: not informed, Weight: not informed*	*Vital signs and pain level compared before and after therapeutic touch (physiotherapists kept their hands on each region for 3 minutes: head, anterior and posterior chest and regions of the body affected). Total time of 20 – 30 minutes*	*Assessment of vital sign variability (HR, RR, temperature), Pain assessment according to NIPS*	*Pain and vital signs declined after intervention (HR, RR)*
Bahman Bijari *et al.*[10]	*Randomized controlled trial,*	*n = 90 NB, GA: 26 - 34 weeks, Weight: 1,200g – 2,000g, Without ventilatory support*	*Tactile stimulation performed 7 to 10 days after birth; interventions conducted twice a day for 5 consecutive days, Randomized into 3 groups: Control Group, Gentle Human Touch Group and Yakson Group*	*Assessment of newborns´ behavioral status according to the ABSS scale*	*The newborns improved behaviorally, especially in the sleep phase, which increased in both the Gentle Human Touch and Yakson Groups*

NB - newborns; GA - gestational age; HR - heart rate; RR - respiratory rate; NIPS - Neonatal Infant Pain Scale; ABSS - Anderson Behavioral State Scale.

Table 2S - Studies included for unimodal auditory stimulation recommendations

Author	Type of study	Sample	Interventions	Main outcomes	Main results
Taheri *et al.*[11]	*Double-blind randomized controlled trial*	*n = 52 NB, GA: 33 ± 4 weeks (Intervention Group), GA: 34 ± 4 weeks (Control Group), Weight: not informed*	*Randomized into 2 groups (n = 26 each):, (1) Intervention Group: submitted to auditory stimulation with lullabies, through earphones, at 50 - 60dB, for 20 minutes, (2) Control Group: earphones with no music (silence). The two groups were observed for 40 minutes*	*HR and SpO_2 assessment*	*Lullaby (male voice and without music) could significantly reduce heart rate and increase blood oxygen saturation of neonates*
Jabraeili *et al.*[12]	*Double-blind randomized controlled trial*	*n = 66 NB, GA: 29 - 34 weeks, Postnatal age ≥ 3 days,, Weight: ≤ 2,800g, Without invasive or noninvasive ventilatory support*	*Randomized into three groups:, (1) Lullabies Sung by the Mother Group (n = 21) , (2) Brahms Lullaby group (n = 25) , (3) Control Group (n = 20): ambient noises. The stimulus was presented at 65 - 70dB, for 15 minutes, between 10am and 7pm, in three consecutive sessions*	*SpO_2 assessment*	*Lullabies sung by the mother and Brahms lullaby music can help to improve SpO_2 in preterm*
Shabani *et al.*[13]	*Randomized crossover clinical trial*	*n = 20 NB, but each infant was studied in two groups of experimental and control. So, totally 40 infants were studied, GA: 29 - 36 weeks, Birth weight: < 2,500g*	*Auditory stimulation was performed with Schwartz´ Transitions music (combination of intrauterine sounds of a pregnant woman and a song sung by a female singer), through speakers placed 20cm from the NB´s ear, at 45 - 60dB, for 15 minutes*	*Physiological responses to pain (HR and SpO_2), Sleep-wake state, Pain level assessed by the NFCS scale*	*Playing music is an effective intervention which decreases the heart rate, sleep–wake state scores, and facial expressions of pain*
Silva *et al.*[14]	*Non-controlled clinical trial*	*n = 12 NB, GA ≤ 36 weeks, Weight: not informed, Spontaneous breathing*	*Auditory stimulation performed with classical music twice a day, for 15 minutes, 1 hour after breastfeeding, for 3 consecutive days, totaling 6 interventions, The music was played inside the incubator at 45 to 55dB, (total noise = intervention + ambient noises), The speakers were placed outside the incubator, in front of the porthole (which remained open during the intervention), but near the NB's head*	*Assessment of HR, RR, SpO_2, BP (systolic and diastolic) and BT*	*Classical music can change the short-term physiological responses of NBs, HR in one of the sessions, but increased it in the next session; besides, it led to the reduction of HR in two sessions and promoted different variations in SatO2 at when compared to the fifth and sixth session of music therapy*

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Keidar *et al.*[15]	*Randomized crossover prospective clinical trial*	*n = 12 NB, GA: 30 - 37 weeks, Tube feeding, Weight: not informed*	*Randomized for auditory stimulation with two types of music (Mozart and Bach) and control (no auditory stimulation), in random sequences, for three consecutive days, The music was always played at midday through speakers placed 30 cm from the NB's ear, at 65 - 70dB, for 30 minutes to one hour after feeding, with the infant in the prone position*	*Primary outcome was resting energy expenditure, However, vital signs (HR, RR and SpO_2) were constantly recorded*	*Auditory stimulation with Mozart music (Mozart Effect) significantly decreased resting energy expenditure*
Amini *et al.*[16]	*Randomized crossover clinical trial*	*n = 25 NB, GA: 29 - 36 weeks, Weight: 1,000g – 2,500g*	*The NBs were randomly submitted to 2 days of classical music (Mozart), two of lullabies and 2 control days (no music), The stimulus was presented through speakers placed 30cm from the NB's ear, for 20 minutes, with the baby in the supine or prone position*	*Assessment of vital signs (HR, RR and SpO_2)*	*Lullabies lowered HR and RR. These effects continued after exposure, Classical music lowered HR, but the effect disappeared after exposure was discontinued, SpO_2 did not change with the intervention*
Loewy *et al.*[17]	*Randomized multicenter controlled trial with blind assessor*	*n = 272 NB, GA ≥ 32 weeks, Weight: not informed*	*All the infants received 3 types of intervention:, (1) Lullabies, (2) Breathing-like sounds (Ocean disc), (3) Heart beat-like sounds (Gato box), Each child received the three stimulation modalities three times a week (in the morning or afternoon), for two weeks, totaling 6 interventions, Auditory stimulation was conducted near the crib or incubator, at 55 - 65dB for 10 minutes, The incubator babies received the intervention through an open porthole, - Control group: did not receive auditory stimulation*	*Primary: vital signs (HR, RR and SpO_2) and activity level, Secondary: feeding behavior (suckings per minute), Sucking behavior (frequency), Sleep pattern, calorie intake*	*The three interventions positively influenced vital signs, sound and lullaby may improve feeding behaviors and sucking patterns and may increase prolonged periods of quiet-alert states and parent-preferred lullabies, sung live, can enhance bonding, thus decreasing the stress parents associate with premature infant care*
Doheny *et al.*[18]	*Within-subject experimental study*	*n = 14 NB, GA: 26 to 32 weeks, and at least 27 weeks of age at the time of the study, Weight: not informed*	*Submitted to routine hospital and maternal sounds (voice and heart beats), inside the incubator/crib, at 55 - 60 dBA, 4 times a day, for 30 minutes, Auditory stimulation with maternal sounds within 7 days of birth and continued until NICU discharge*	*Frequency of adverse cardiorespiratory events (apnea > 20 seconds and/or HR decrease to below 100bpm for babies < 34 gestational weeks or below 80bpm for infants > 34 gestational weeks)*	*Cardiorespiratory events declined with age., Frequency was lower with exposure to maternal sounds. This effect was significant in infants with GA ≥ 33 weeks, suggesting a therapeutic window*
Olischar *et al.*[19]	*Randomized controlled trial*	*n = 20 NB, GA: ≥ 32 weeks, Weight: not informed, Neurologically healthy during the first 6 weeks of life, without ventilatory support*	*Randomized into 2 groups (n = 10 each):, (1) Experimental Group: submitted to Brahms' lullabies, through speakers placed 30cm from the NB's head inside the incubator, at 50 - 55 dBA for 20 minutes, (2) Control Group: no auditory stimulation with music*	*Assessment of aEEG activity:, Background pattern, sleep-wake cycle quality and periods of restful sleep in terms of frequency, duration and minimum and maximum amplitudes*	*There were no statistically significant intergroup differences; however, the small sample was small*
Tramo *et al.*[20]	*Randomized prospective controlled trial*	*n = 13 NB, GA: 30 weeks and 6 days to 34 weeks and 3 days, Weight: 1,200g – 2,600g at 1 to 35 days of life, without ventilatory support or oxygenation*	*Randomized into 2 groups:, (1) Intervention Group (n = 7): submitted to auditory stimulation with lullabies, through speakers placed 50cm from the infant's head, inside the incubator, at 70 dBA for 10 minutes, (2) Control Group (n = 6): no auditory stimulation with music*	*Assessment of physiological responses (HR, RR and SpO_2) and behavioral assessment (opening the eyes, head movements and crying) before, during and after heel puncture*	*In both groups, HR and RR increased during the heel puncture procedure and nearly all the infants cried, During the 10-minute recovery period following heel puncture, HR and crying decreased significantly in the intervention group*
Yildiz *et al.*[21]	*Quasi-experimental prospective study*	*n = 90 NB, GA: 30 - 34 weeks and exhibiting no sucking reflex, Weight: ≥ 1,000g, Tolerating enteral diet*	*Allocated to 3 groups (N = 30/each):, (1) Control Group: no intervention, (2) Sucking Group: the babies were given pacifiers, (3) Lullaby Group: Lullabies were played to the babies through speakers. placed at the infants' feet in the incubator, at 65dB, during force feeding*	*Assessment of peak HR, RR, and SpO_2 before, during and after feeding, body weight, sucking success, transition period to oral feeding, and hospitalization time*	*The pacifier group proceeded to total oral feeding faster, followed by the Lullaby Group, Sucking success was achieved by the pacifier group, followed by the Lullaby Group, The pacifier group had the shortest hospitalization time, followed by the Lullaby Group, There was no difference in RR, SpO_2 and weight between the 3 groups*
Alipour *et al.*[22]	*Double-blind randomized placebo-controlled clinical trial*	*N = 90 NB, GA: 28 - 36 weeks and 1 to 25 days of life, Weight: not informed*	*Randomized into 3 groups (n = 30 each):, (1) Intervention: auditory stimulation with lullabies, at 50 - 60 dB, through earphones, for 20 minutes, with the NB in the supine position, (2) Silence Group (placebo): NB in the supine position with earphones for 20 minutes, without music, (3) Control Group: no intervention; routine care*	*Physiological responses (HR, RR and SpO_2), Behavioral responses assessed by the BSI scale*	*No significant intergroup differences in terms of physiological and behavioral responses,*

NB - newborns; GA- gestational age; HR - heart rate; SpO_2 - blood oxygen saturation; NFCS - Neonatal Facial Coding System; RR - respiratory rate; BP - blood pressure; BT - body temperature; NICU - neonatal intensive care unit; aEEG - amplitude-integrated electroencephalogram; BSI - Behavioral State Instrument.

Table 3S - Studies included for unimodal olfactory stimulation recommendations

Author	Type of study	Sample	Interventions	Main outcomes	Main results
Edraki *et al.*[23]	Randomized prospective controlled clinical trial	n = 36 premature NB, GA: 33 - 35 weeks , Weight: < 2,500g	Randomized into two groups (18 NB in each group):, Control Group: submitted to routine care, Intervention Group: olfactory stimulation with vanillin solution	Frequency of apnea episodes, arterial blood oxygen saturation and HR	There was a reduction in apnea episodes in the group submitted to vanillin solution, There was no change in vital signs between groups
Baudesson de Chanville *et al.*[24]	Double-blind randomized placebo-controlled clinical trial	n = 33 NB, GA: 30 - 36 weeks , Weight: > 1,500g	Randomized into two groups: , Control Group: 17 NB submitted to routine care , Intervention Group: 16 NB Olfactory stimulation with maternal milk 10 days after birth	Pain assessment using PIPP and changes in vital signs (HR & SPO2) of NBs submitted to venipuncture	Significant pain reduction without changes in vital signs
Marom *et al.*[25]	Randomized prospective controlled clinical trial	n = 20 NB, GA: 32 - 35 weeks , Weight: not informed , Without ventilatory support	Olfactory stimulation with vanillin odour exposureversus no vanillin odour exposure for 2 consecutive days	Metabolic rate evaluated through indirect calorimetry; oxygen (VO_2) and carbon dioxide (VCO_2) consumption	There was no difference between the two groups in terms of resting energy expenditure,
Romantsik *et al.*[26]	Randomized prospective controlled clinical trial	n = 69 NB, GA: ≤ 37 weeks , Weight: 3,000g – 4,000g	Randomized into two groups: , Control Group: 30 NB submitted to water scent (7cm from the nose) for 3 minutes, Intervention Group: 39 NB olfactory stimulation with vanilla scent (7cm from the nose) for 3 minutes	Responses to painful procedures with vanilla and water scents were measured using two scales, the NFCS and BIIP, along with crying duration and hand movements	There were no statistically significant differences between stimulation with vanilla scent compared to water use for the reduction of pain after painful procedures

NB - newborn; GA - gestational age; HR- heart rate; PIPP - premature infant pain profile; SpO_2 - blood oxygen saturation; VO_2 – maximum oxygen volume; VCO_2 – maximum carbon dioxide volume; NFCS - Neonatal Facial Coding System; BIIP - Behavioural Indicators of Infant Pain.

Table 4S - Studies included for unimodal gustatory stimulation recommendations

Author	Type of study	Sample	Interventions	Main outcomes	Main results
Bernardini *et al.*[27]	Randomized prospective controlled clinical trial	n = 28 NB, GA: 30 - 35 weeks, Weight: not disclosed	Glucose solution associated to no nutritive suction versus sensorial saturation (14 each) comprising a 6-step protocol:, Keep the NB in lateral position, Maintain eye contact, Massage face and back, Talk to the baby gently but firmly, Allow child to smell the fragrance of a baby oil (Babygella, Guieu Labs) on the therapist's hands place 10% glucose on the baby's tongue	Assess pain level during venipuncture using the PIPP scale	Sensorial saturation ameliorates the quality of life in NICU and reduces the pain threshold perceived by newborn
Bueno *et al.*[28]	Randomized prospective controlled clinical trial	n = 113 NB, GA: 34 - 36 weeks, Weight: ≥ 2,000g	Stimulation with maternal milk versus glucose	Evaluate pain level by comparing stimulation with maternal milk versus glucose, before NB heel puncture, using the PIPP	No statistically significant differences were found between the interventions
Cignacco *et al.*[29]	Randomized prospective multicenter controlled clinical trial	n = 71 NB, GA: 24 - 32 weeks, Weight: not disclosed	Stimulation with sucrose, facilitated tucking, and a combination of both interventions during heel puncture and collected during the first 14 days of their NICU stay	Assess pain level by comparing sucrose versus assisted suction, during heel puncture of NBs, using the BPNS score (combination of items that evaluate physiological and behavioral status)	Sucrose, regardless of association, showed better efficacy in reducing pain
Mekkaoui *et al.*[30]	Randomized prospective controlled clinical trial	n = 125 NB, GA: 28 - 37 weeks, Weight: not disclosed	Randomized into five non-pharmacological interventions: , Oral glucose stimulation , Non-nutritive sucking , Oral administration of glucose 30%; associated with pacifier suction, Oral administration of glucose 30%; associated with formula milk, Oral administration of age-appropriate formula milk	Assess pain level during heel puncture using the DAN scale	Among the five groups, NB who received 30% glucose, artificial milk, or sucking a pacifier showed better results
Ou-Yang *et al.*[31]	Randomized prospective controlled clinical trial	n = 123 NB, IG: < 37 weeks, Weight: not disclosed	Stimulation with distilled water (n = 48) versus 25% glucose water (n = 50) versus maternal milk (n = 62)	Assess pain level during heel puncture using the PIPP scale	Stimulation with maternal milk decrease pain level
Costa *et al.*[32]	Randomized prospective controlled clinical trial	n = 124 NB, GA: ≤ 32 weeks, Weight: ≤ 1,500g	Administration of a 1mLdose of 25% glucose solution 2 minutes before and immediately after the first retinopathy of prematurity (ROP) eye examination	Evaluate pain intensity during the first eye examination for retinopathy of prematurity in NB using the NPAS scale	Glucose decreases the pain level of the first eye examination for retinopathy of prematurity

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Nimbalkar *et al.*[33]	*Randomized prospective controlled clinical trial*	*n = 104 NB , GA: > 28 weeks, Weight: not disclosed*	*One group received lingual dextrose before orogastric tube placement and the other received a placebo*	*Evaluate pain reduction after orogastric tube placement, with lingual administration of 25% dextrose, using the PIPP scale*	*Lingual dextrose administration decreases pain level compared to the placebo group*
Pandey *et al.*[34]	*Randomized prospective controlled clinical trial*	*n = 105 NB, IG: < 37 weeks (< 168 hours of life), Weight: not disclosed*	*Stimulation with 24% sterile sucrose solution (n = 53) versus distilled water (n = 52), both administered orally 2 minutes before orogastric tube placement*	*Evaluate pain level following orogastric tube placement using the PIPP scale*	*Sucrose reduced pain level compared to the placebo group*
Sahoo *et al.*[35]	*Randomized prospective controlled clinical trial*	*n = 160 NB, GA: > 34 weeks, Weight not disclosed*	*Three groups randomized into: , Stimulation with maternal milk (n = 50), 25% dextrose (n = 62), Sterile water (n = 48)*	*Assess pain level after venipuncture using the PIPP scale and changes in HR, SpO_2 and duration of crying*	*Dextrose and maternal milk reduced pain level compared to the placebo group*
Scaramuzzo *et al.*[36]	*Randomized prospective controlled clinical trial*	*n = 158 NB, GA: > 37 weeks, Weight: not disclosed*	*Randomized into two groups: stimulation with oral sucrose (n = 82) versus wrapping (n = 76)*	*Evaluate spontaneous fluctuations in skin conductance to measure pain and to compare oral sucrose with non-apharmacological analgesic packaging*	*Oral sucrose is more effective in reducing pain level*
Al Qahtani *et al.*[37]	*Randomized prospective controlled clinical trial*	*n = 90 NB, GA: > 38 weeks, Weight: not disclosed*	*Stimulation with EMLA cream (n = 30) versus oral sucrose (n = 30) versus combination of EMLA cream and oral sucrose (n = 30)*	*Assess pain level comparing EMLA use and oral sucrose in NBs during circumcision*	*The combination of sucrose with EMLA cream has the greatest analgesic effect*
Dilli *et al.*[38]	*Randomized prospective controlled clinical trial*	*n = 64 NB, GA: 28 - 37 weeks, Weight: not disclosed*	*Stimulation with sucrose on pacifier (n = 32) versus sucrose-free pacifier versus sterile water (n = 32) 30 seconds before eye examination*	*Evaluate effectiveness of oral sucrose combined with non-nutritive sucking to reduce pain level*	*Sucrose combined with non-nutritive sucking reduces pain level during eye examinations*
Ravishankar *et al*[39]	*Randomized prospective controlled clinical trial*	*n = 150 NB, GA: > 34 weeks, Weight: not disclosed*	*Randomization into 3 groups: stimulation with 25% dextrose (n = 50) versus 10% dextrose (n = 50) versus distilled water (n = 50), 2 minutes before nasogastric tube placement*	*Assess pain level using the PIPP scale, crying duration, and changes in heart rate*	*25% oral dextrose reduces pain level before nasogastric tube placement*
Suhrabi *et al.*[40]	*Randomized prospective controlled clinical trial,*	*n = 90 NB, GA: > 37 weeks, Weight: not disclosed*	*Randomization into three groups: stimulation with glucose (n = 30) versus oral sucrose (n = 30) versus placebo (n = 30), 2 minutes before vaccination*	*Assess pain intensity before the Hepatitis B vaccination using the NIPS scale*	*Both glucose and sucrose are equally effective in decreasing pain when administered before the Hepatitis B vaccination*
Uzelli *et al.*[41]	*Randomized prospective controlled clinical trial*	*n = 80 NB, GA: > 33 weeks, Weight: not disclosed*	*Oral glucose administration (n = 40) versus control group (n = 40) 2 minutes before intramuscular injection*	*Assess pain intensity using the NIPS scale*	*Oral glucose, even when used in low amounts, is effective in reducing pain before intramuscular injection*
Kataria *et al.*[42]	*Randomized prospective controlled clinical trial*	*n = 24 NB, GA: > 31 weeks, Weight not disclosed*	*Administration of 2mL dextrose (n = 12) versus control group (n = 12 PTNBs) 2 minutes before retinopathy of prematurity corrective laser surgery*	*Assess pain intensity using the PIPP scale before and 30 seconds after starting the laser treatment*	*A single dose of oral dextrose did not significantly reduce pain during laser treatment in premature neonates*
Tutag Lehr *et al.*[43]	*Randomized prospective controlled clinical trial*	*n = 56 NB, IG: > 37 weeks (≤ 7 days of life), Weight: not disclosed*	*Randomized into 2 groups: stimulation with 24% sucrose (n = 29) versus sterile water (n = 27) 10 minutes before heel puncture*	*Assess pain and blood flow, in NB under the effect of oral sucrose, using laser doppler and NIPS scale*	*Blood flow and pain after heel puncture were less in NB who received 24% sucrose*
Vezyroglou *et al.*[44]	*Randomized prospective controlled clinical trial*	*n = 32 NB, GA: < 37 weeks, Weight: > 1,500g*	*Randomized into 2 groups: stimulation with glucose (n = 16) versus placebo group (n = 16), 3 minutes before oropharyngeal aspiration*	*Evaluate pain level using the PIPP scale*	*Pain level did not differ between the two groups*
Medeiros *et al.*[45]	*Randomized prospective controlled clinical trial*	*n = 90 NB, GA: 28 - 36 weeks, Weight: not disclosed*	*Randomization into 2 groups: stimulation with water (n = 46) versus sucrose (n = 44) to analyze specific hand-to-mouth and hand sucking behaviors*	*Assess motor behavior and behavioral status of NB by observing hand-to-mouth and hand sucking behavior*	*Oral stimulation had a positive influence on hand-mouth coordination, regardless of the stimulus (water or sucrose)*

NB - newborn; GA - gestational age; PIPP - Premature Infant Pain Profile; NICU - neonatal intensive care unit; BPNS - Bernese Pain Scale Neonatal Scale; DAN - Douleur Aigue Nouveau ne scale; ROP - retinopathy of prematurity; NPAS - Neonatal Pain, Agitation and Sedation; HR - heart rate; SpO_2- blood oxygen saturation; NIPS - Neonatal Infant Pain Score; PTNB – preterm newborn.

Table 5S - Studies included for multimodal tactile-kinesthetic stimulation recommendations

Author	Type of study	Sample	Interventions	Main outcomes	Main results
Ahmed *et al.*[46]	*Prospective quasi-experimental clinical trial*	*n = 151 NB, GA: 30 - 37 weeks , Weight: 1,000g – 1,200g , Without ventilatory support*	*Randomized into two groups:, - Control Group: 76 NB submitted to routine care, - Intervention Group: 75 NB submitted to tactile-kinesthetic stimulation for 15 minutes (3 times a day for 7 consecutive days)*	*Weight gain and length of hospital stay*	*Tactile kinesthetic group had greater weight gain and shorter length of hospital stay compared to the control group*
Smith *et al.*[47]	*Randomized prospective double-blind placebo-controlled clinical trial*	*n = 21 NB, GA: 30 - 31 weeks , Weight: 1,500g*	*Randomized into two groups: , Control Group: 11 NB, therapists stood beside the incubator for 20 minutes twice a day, Intervention Group : 10 NBs submitted to 20 minutes of massage + kinesthetic movement (Moyer-Mileur) twice a day*	*Autonomic nervous system function during sleep stages and assistive care, measured by HRV after 2 weeks of massage therapy performed twice a day*	*There was no difference in HRV between intervention group and control group*
Smith *et al.*[48]	*Randomized prospective single-blind controlled clinical trial*	*n = 21 NB, GA: 29 - 32 weeks , Weight: 1,500g*	*Randomized into two groups: , Control Group: 20 NB, therapists stood beside the incubator for 20 minutes twice a day, Intervention Group: 17 NB, 20 minutes of massage + kinesthetic movement (Moyer-Mileur) twice a day for 4 weeks*	*Heart rate variability through ECG*	*Massage improved the sample's autonomic nervous system function*
Haley *et al.*[49]	*Randomized prospective single-blind controlled clinical trial*	*n = 40 NB, GA: < 37 weeks, Weight: 1,500g – 1,600g*	*Randomized into two groups: , Control Group: 20 NB are placed in a supine position without tactile stimulation and without kinesthetic , TKS Group: movement tactile/kinesthetic stimulation: 20 NB, 20 minutes of massage twice daily, 6 days per week for 2 weeks, TKS = (1) legs from top of thighs to ankles and feet, (2) chest over ribcage, (3) shoulders to hands, (4) head from crown to neck and including face, (5) back from neck to waist (performed with infant remaining in supine position)*	*Increase in anthropometry; in the quantitative measurement of the ultrasound-assessed tibial speed of sound; urine and blood markers*	*TKS improved bone strength; bone metabolism biomarkers suggest improved bone mineralization in the massage group.*
Aliabadi *et al.*[50]	*Randomized prospective controlled clinical trial*	*n = 40 NB , GA: 29 - 32 weeks , Weight: > 1,500g and < 2,499g*	*Randomized into two groups: , Control Group: 20 NB; , Intervention Group: 20 NB submitted to 15-minutes interventions divided into three phases: 5 minutes massage + 5 minutes. TKS + 5 minutes massage (field protocol), 3 times daily for 10 consecutive days*	*Behavioral state assessment*	*The group that received TKS showed better motor and regulation state*
Chen *et al.*[51]	*Randomized prospective controlled clinical trial*	*n = 42 NB, GA: 37 - 41 weeks , Weight: 2,800g to 3,600g*	*Randomized into two groups: , Control Group: 22 NB , Intervention Group: 20 NB submitted to 15 to 20-minute interventions (touch therapy by field protocol), performed twice daily for 5 consecutive days*	*Assessment of bowel movement frequency, measurement of transcutaneous jaundice and serum bilirubin levels*	*The group that received massage (touch therapy by field protocol), showed lower bilirubin levels*
Guzzetta *et al.*[52]	*Randomized prospective controlled clinical trial , ,*	*n = 20 NB, GA: 30 - 33 weeks, Stable hospitalized NB , Weight: between the 25th and 75th percentile*	*Randomized into two groups: , Control Group: 10 NB, Intervention Group: 10 NB submitted to 15-minutes interventions divided into two phases: 10 minutes massage + 5 minutes. Kinesthetic movement, performed 3 times daily for 5 consecutive days over a period of 2 weeks (two-day interval between weeks)*	*ECG assessment of brain electrical activity*	*Massage favored a maturation process of brain electrical activity similar to that observed in utero*
Ferreira *et al.*[53]	*Randomized prospective controlled clinical trial*	*n = 32 NB, GA: 31 - 33 weeks , Weight: < 2,500g*	*Randomized into two groups: , Control Group: 16 NB , Intervention Group 16 NBs submitted to TKS*	*Assessment of behavioral state*	*TKS contribute towards adjustment and self-regulation of behaviour*
Ho *et al.*[54]	*Randomized prospective controlled clinical trial*	*n = 20 NB, GA: < 34 weeks , Weight: < 1,500g*	*Randomized into two groups: , Control Group: 12 NB received similar duration of light still touch , Intervention Group: 12 NB received massage therapy starting at 34 weeks post-conceptional age (15 minutes daily, 5 days/week for 4 weeks)*	*Assessment of motor performance using the TIMP scale*	*Improvement in motor performance (NB with low TIMP score before intervention); shorter length of hospital stay for intervention group*

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Moyer-Mileur *et al.*[55]	*Randomized prospective single-blind controlled clinical trial*	*n = 44 NB, GA: 29 - 32 weeks , Weight: 1,300g – 1,800g*	*Randomized into two groups: , Control Group: 22 NB, therapists stood beside the incubator twice a day, Intervention Group: 22 NBs submitted to interventions of 20 minutes, divided into massage + TKS, twice daily for 6 consecutive days over a period of 4 weeks (Moyer-Mileur Protocol)*	*Evaluate weight gain and fat deposition*	*massage may improve body fat deposition, and in turn growth quality, of preterm infants in a sex-specific manner*
Ang *et al.*[56]	*Randomized prospective controlled clinical trial*	*n = 120 NB, GA: 30 weeks , Weight: 600g – 1,800g*	*Randomized into two groups: , Control Group: 62 NB, Intervention Group: 58 NB submitted to interventions of 5 to 15 minutes, divided into three phases: 5 minutes. massage + 5 minutes. TKS + 5 minutes. massage (field protocol) 3 times daily for a minimum of 5 days (maximum of 4 weeks or until hospital discharge)*	*Assessment of massage effects on the immune system*	*Increase in white blood cells and greater weight gain in the intervention group*
Diego *et al.*[57]	*Randomized prospective controlled clinical trial*	*n = 30 NB , GA: 28 - 32 weeks stable hospitalized NB , Weight: 1,000 – 1,500g*	*Randomized into two groups: , Massage Group: 15 NB submitted to massage movements three times a day for 10 minutes over 5 days, TKS Group: 15 NB submitted to limb flexion /extension 3 times a day for 10 minutes over 5 consecutive days (field and Moyer-Mileur adapted protocol)*	*Assessment of vagal activity (ECG in the first week of intervention) and calorie consumption*	*Increase in weight gain in the intervention group*

NB - newborn; GA - gestational age; HRV – heart rate variation; ECG – electrocardiogram; TKS - tactile/kinesthetic stimulation group; TIMP - Test of Infant Motor Performance.

Table 6S - Studies included for multimodal massage stimulation recommendations

Author	***Type of study***	***Sample***	***Interventions***	***Main outcomes***	***Main results***
Kumar *et al.*[58]	*Randomized controlled clinical trial*	*n = 44 , GA: < 35 weeks, Weight: < 1,800g*	*Two groups: , 23 in the control group , 25 submitted to massage therapy using oil on both shoulders starting from the neck with baby in prone position, then the upper back to hip area followed by the upper and lower limbs, one at a time in supine position for 10 minutes, 4 times daily over a period of 28 consecutive days*	*Weight gain; serum triglyceride level; length and head circumference*	*The massage group presented weight gain after 28 days and decreased weight loss within the first 7 days. There was no statistical difference regarding the other outcomes*
Seaedi *et al.*[59]	*Randomized controlled clinical trial*	*n = 121, GA: < 37 weeks, Weight: not disclosed*	*Three groups:, Massage therapy group with oil (n = 40), Massage therapy (n = 40), Control group (n = 40), 5 minutes of massage 4 times a day for 7 days*	*Weight gain*	*There was greater weight gain in the oil massage therapy group compared to the other 2 groups*
Fallah *et al.*[60]	*Randomized controlled clinical trial*	*n = 57, GA: 33 - 37 weeks*	*Two groups: , Group 1: only moderate pressure massage therapy (n = 17), Group 2: massage therapy with moderate pressure and oil (n = 17)*	*Weight gain on day 14, 1 and 2 months after the interventions*	*The group submitted to massage oil therapy exhibited greater weight gain in all assessments compared to the other group*
Basiri Moghadam *et al.* [61]	*Randomized controlled clinical trial,*	*n = 40, GA: 34 - 36 weeks, Weight: not disclosed*	*Two groups: , 20 controls, 20 underwent massage therapy. Type of massage therapy not disclosed. Intervention time: 20 minutes twice a day for 4 consecutive days*	*Number of bowel movements; transcutaneous bilirubin level*	*The massage therapy group had a higher number of bowel movements and lower transcutaneous bilirubin levels*
Lin *et al.*[62]	*Randomized controlled clinical trial*	*n = 56, GA: 30 - 40 weeks, Weight: not disclosed*	*Two groups: , Control Group (n = 29), Massage Therapy group (n = 27)*	*Length of hospital stay; weight gain; increased bowel movement frequency; microbilirubin level*	*There was an increase in bowel movement frequency and a decrease in bilirubin levels in the massage group; there was no difference between the groups for the other outcomes*
Dalili *et al.*[63]	*Randomized controlled*	*n = 50, GA: 36 - 40 weeks, Weight: not disclosed*	*Two groups:, Control Group (n = 25), Massage Group (n = 25)*	*Increased bowel movement frequency; transcutaneous bilirubin level*	*There was a decrease in bilirubin levels in the massage group. There was an increase in bowel movement frequency in the control group on day 1. On the subsequent days, there was no difference between the two groups*
Chik *et al.*[64]	*Randomized controlled clinical trial*	*n = 80, GA: 30 to 40 weeks*	*Two groups: , Control Group (n = 40), Massage Group (n = 40): upper limb massage before and after venipuncture*	*Pain level reduction assessed by PIPP*	*There was a reduction in pain score in the group submitted to massage therapy*
Yates *et al.*[65]	*randomized cross-over study*	*n = 23, GA: 32 - 48 weeks, Weight: not disclosed*	*Two groups: , Massage therapy the first day (n = 13), Massage therapy the second day (n = 10)*	*Massage therapy can be used as an adjunct intervention to induce sleep*	*Massage therapy did not induce sleep immediately after massage and infants are more wakeful following massage therapy*

GA - gestational age; PIPP - Premature Infant Pain Profile.

Table 7S - Studies included for multisensory skin-to-skin stimulation recommendations

Author	Type of study	Sample	Interventions	Main outcomes	Main results
Azevedo *et al.* [66]	*Quasi-experimental study design*	*n = 43, GA: > 29 weeks , Weight: not disclosed, Hemodynamically stable, intubated receiving MV*	*A group evaluated longitudinally on 3 occasions: before, during and after the procedure for a duration of 90 minutes*	*Procedure safety, Variables measured: HR, SpO_2, FiO2, mean arterial blood pressure, and temperature*	*Changes in the variables studied were not clinically significant (< 5% from baseline) although statistically significant. Skin-to-skin contact is a safe procedure for NBs receiving MV*
Carbasse *et al.* [67]	*Quasi-experimental study design study*	*n = 96 , GA: 24 - 33 weeks, Weight: > 500g, Vulnerable preterm infants*	*Vital signs, body temperature, and oxygen requirement data were prospectively recorded by each infant's nurse before (baseline), during (3 time points), and after their first skin-to-skin contact. , 17 clinically stable NBs receiving MV, 49 with nasal CPAP and 30 spontaneously breathing room air*	*Safety and physiological effectiveness of the procedure, Evaluate the impact of the respiratory support. Variables measured: HR, SpO_2, FiO2, transcutaneous partial pressure of carbon dioxide ($TcPCO_2$), and temperature*	*Changes in the variables studied were statistically significant , Skin-to-skin contact is an effective and safe procedure for vulnerable preterm infants*
Karlsson *et al.* [68]	*Quasi-experimental study design*	*n = 27, GA = 22 to 26 weeks , Weight: not disclosed*	*Infants' skin temperature and body temperature, ambient temperature, and relative humidity were measured during pretest (in incubator), test (during SSC), and posttest (in incubator) periods*	*Assessment of the NICU's thermal balance and physical care environment during skin-to-skin, Variables studied: Relative humidity and air temperature in the incubator and skin-to-skin environment; corporal temperature; skin temperature; evaporimetry (transepidermal water loss and insensible water loss)*	*Early skin-to-skin initiation allows thermoregulation to occur in even the smallest NBs receiving intensive care, including mechanical ventilation , Skin-to-skin is an important and safe care mode for extreme PTNBs, even with mechanical ventilation*
Lorenz *et al.* [69]	*Prospective observational non-inferiority study*	*n = 40, GA < 33 weeks, Weight: > 800g, Receiving ventilatory support (ETT, CPAP or HFNC)*	*rcO2 was measured using near-infrared spectroscopy. Ninety minutes of skin-to-skin contact, with infants in incubators acting as their own control*	*Evaluate rcO2 on two occasions (skin-to-skin contact, and incubator care). Secondary outcomes included physiological parameters (SpO_2, HR, FiO2, cFTOE and AT) evaluated on both occasions and divided by ventilatory support modality.*	*Cerebral oxygenation and other physiological measurements in ventilated preterm infants did not differ between skin-to-skin contact, and incubator care*
Park *et al.* [70]	*Prospective clinical trial,*	*n = 31, GA: 25 - 32 weeks, Weight: 760g – 1,740g*	*Two groups submitted to skin-to-skin contact: 25 - 28 weeks (n = 11) and 29 - 32 weeks (n = 20)*	*Determine the clinical characteristics and safety of skin-to-skin contact according to GA, Physiological parameters were evaluated longitudinally for 60 minutes (15 minutes before, 30 minutes during and 15 minutes after the procedure). , Variables studied: HR, RR, SpO_2, blood pressure, temperature*	*Changes in the variables studied were not clinically significant (< 5% from baseline) although some were statistically significant. , At the same post-menstrual age, the lower GA group showed greater thermoregulation maturation compared to the higher GA group, Skin-to-skin contact is a safe procedure for PTNBs even while receiving ventilatory support*
Okan *et al.* [71]	*Randomized controlled clinical trial, ,*	*n = 107, GA: > 37 weeks, Age between 24 and 48 hours of life, Weight: not disclosed, Healthy NB,*	*Three groups:, Skin-to-skin contact group (N = 35) with maternal breast feeding;, n = 36 skin-to-skin contact, n = 36 placed in the crib, evaluated before, during and after the painful stimulus,*	*Evaluate the effectiveness of skin-to-skin contact for pain reduction during heel puncture in FTNBs, Assess whether the combination of skin-to-skin contact with breastfeeding provides greater analgesia than skin-to-skin contact alone, Variables studied: Crying time after painful stimulus. Secondary outcomes: HR, SpO_2*	*HR, SpO_2, and crying duration was significantly lower in the groups skin-to-skin and skin-to-skin contact with breastfeeding, compared to NBs in the crib who underwent the painful procedure, Skin-to-skin contact before, during, and after a painful stimulus promotes a reduction in physiological and behavioral responses to pain in healthy FTNBs, The combination of skin-to-skin contact with breastfeeding promotes an analgesic effect similar to skin-to-skin contact only*

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Saeidi *et al.* [72]	*Randomized controlled clinical trial*	*n = 60, GA: healthy full-term NBs, Weight: not disclosed*	*Two groups: skin-to-skin contact for 30 minutes (n = 30) and control (wrapped in blanket and placed next to mother, n = 30)*	*Evaluate the effect of skin-to-skin contact on pain intensity using the NIPS scale in healthy NBs undergoing a painful procedure (vaccination), Secondary outcomes: HR, SpO_2 and crying duration*	*Mean pain intensity during the procedure, and 3 minutes after, was significantly lower in the skin-to-skin contact group, Kangaroo care may be used to decrease pain intensity in newborns undergoing painful procedures*
Cong *et al.* [73]	*Randomized crossover clinical trial*	*n = 28, GA: 28 - 32 weeks, Weight: not disclosed, < 14 days of life in heated incubator*	*Three groups randomized into different procedure sequences, evaluated on 6 occasions: skin-to-skin for 30 minutes, skin-to-skin for 15 minutes, and standard care*	*Skin-to-skin effect (duration of 30 and 15 minutes) on the autonomic pain response of PTNBs subjected to heel puncture compared to standard care. , Variables studied: HR variability, behavioral state*	*Both skin-to-skin contact durations, before and during heel puncture, promote prolonged restful sleep after puncture. , Kangaroo care has a significant effect on reducing autonomic pain responses in preterm infants. The findings support that KC is a safe and effective pain intervention, in the neonatal intensive care unit*
Nimbalkar *et al.*[74]	*Randomized controlled clinical trial*	*n = 100 term and late preterm, Weight: > 1,800g*	*Two groups:, Intervention Group: SSC at 30 minutes to 1 hour after delivery and continue for as long as possible in the first 24 hours with each session lasting for minimum 60 minutes, Control Group, after providing routine care under radiant warmer, NBs were kept clothed (including head cap) and covered with blanket with their mother (bedding in) for first 48 hours*	*Temperature and heart rate*	*The incidence of hypothermia in conventional care was significantly higher as compared with the SSC*
Chidambaram *et al.*[75]	*Randomized crossover clinical trial*	*n = 100, GA: 32 - 36 weeks, Weight: < 2,500g, Hemodynamically stable without dependence on oxygen.*	*Two groups: , Control Group (n = 50), Skin-to-Skin Contact Group (n = 50),*	*PIPP pain scale assessment 15 minutes before, 15 and 30 minutes after heel puncture*	*PIPP scores at 15 and 30 minutes after puncture were significantly lower in the skin-to-skin contact group compared to the control group, Skin-to-skin contact is effective in reducing pain in PTNBs subjected to heel puncture*
Gao *et al.* [76]	*Randomized controlled clinical trial*	*n = 75, GA: < 37 weeks, Weight: 2,030g*	*Two groups: , Control group (n = 37), Skin-to-Skin Group (n = 38)*	*Evaluate the effectiveness of 30 minutes of skin-to-skin contact on behavioral and physiological responses of PTNBs undergoing heel punctures. During the first puncture procedure, all NBs were kept in the incubator. In the other three procedures, the NBs were randomized into skin-to-skin contact or standard incubator care; evaluators were blinded to the purpose of the study. , Variables studied: facial expression, crying, and HR in four heel puncture procedures*	*HR was significantly lower, crying and grimacing duration was significantly shorter (from time of heel puncture to recovery) across repeated heel puncture procedures in the skin-to-skin group compared to the control group, The effect of repeated Kangaroo Mother Care analgesia remains stable in preterm infants over repeated painful procedures*
Choudhary *et al.*[77]	*Quasi-experimental crossover single-blind clinical trial*	*n = 140, Weight: > 1,000g*	*One group (n = 140): each NB was its own control, GA < 37 weeks , All NBs were divided into gestational age: 28 - 30 weeks (n = 80); 30 - 34 weeks (n = 60) and birth weight: 1,000g – 1,500 g (n = 88); 1,500 – 2,500g (n = 52)*	*Assessment of PIPP during heel puncture, HR, SpO_2, crying duration and recovery time,*	*The effect of skin-to-skin contact was statistically significant in the PTNBs (30 - 34 weeks) and very low weight (1,000 – 1,500g) groups, SpO_2 drop was lower (36% reduction) in the skin-to-skin contact group than in conventional care, Crying duration was shorter in the skin-to-skin contact group than in conventional care, with a statistically significant difference, PIPP scores were significantly lower with skin-to-skin contact, Implementing skin-to-skin contact is a safe method of helping physiological and behavioral stability in PTNBs*

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Kaffashi *et al.* [78]	*Randomized quasi-experimental crossover clinical trial*	*n = 134 NBs (8 PTNBs), Received 8 weeks of skin-to-skin contact.*	*Three groups: PTNBs received skin-to-skin contact for 8 weeks (16 EEG recordings during sleep, n = 8) compared to two groups (nN = 126): one group of PTNBs with corrected gestational age and another of FTNBs*	*Neurophysiology maturation of the neonatal brain by quantifying temporal characteristics (regularity and predictability) of sleep EEG signals, , ,*	*The group of PTNBs that received skin-to-skin contact exhibited more complex EEG signals compared to PTNBs of the same gestational age, Discriminatory analyses show that PTNBs who received skin-to-skin contact (at 40 weeks corrected age) exhibit patterns closer to FTNBs than PTNBs not submitted to this intervention, at the same gestational age.*
Neu *et al.* [79]	*Randomized controlled clinical trial*	*n = 79, GA: 32 - 35 weeks, Weight: not disclosed*	*Three groups: , Control Group (n = 24), Skin-to-Skin Contact Group (n = 29), Group Wrapped in Blanket (n = 26*	*Evaluate coregulation in salivary cortisol between mother and NB; coregulation defined as progressive reduction in the absolute difference between mother and NB cortisol levels during each 60-minute session of skin-to-skin contact, Variable studied: coregulation of salivary cortisol between mother and NB*	*Decreased cortisol levels in mothers and NBs suggesting that skin-to-skin contact caused a decline in stress hormone levels, There was no significant difference in coregulation between the groups, nonstressful situations, co-regulation in salivary cortisol may not differ based on holding method*
Srivastava *et al.* [80]	*Randomized controlled clinical trial*	*n = 240, GA: any age, Weight > 2,500g, Skin-to-skin in the first 30 minutes of life*	*Two groups: , Control Group (n = 118), Skin-to-Skin Contact Group (n = 122), Variables studied: breastfeeding effectiveness, 6-week breastfeeding status, maternal satisfaction, thermoregulation, weight loss at hospital discharge and at first follow-up, and morbidity*	*Evaluate the impact of early skin-to-skin initiation on breastfeeding effectiveness and maternal satisfaction in relation to perceived NB breastfeeding status at hospital discharge, Secondary outcomes: related to neonatal well-being (thermoregulation in the immediate postpartum period, NB weight parameters and morbidities during the first six weeks of life)*	*Skin-to-skin contact contributed to greater breastfeeding effectiveness, more infants being exclusively breastfed at the first follow-up and at 6 weeks, greater maternal satisfaction, better immediate postpartum temperature gain, lower weight loss at hospital discharge and first follow-up, and lower morbidity when compared to the control group*
Jayaraman *et al.* [81]	*Randomized controlled clinical trial, ,*	*n = 160, Weight: 1,000g – 1,800g,*	*Two groups: early skin-to-skin contact initiated within the first 4 days of life (n = 80); late skin-to-skin contact, initiated after complete stabilization, defined as absence of respiratory support and intravenous fluids (n = 80)*	*Evaluate the effects of early skin-to-skin contact initiation on exclusive breastfeeding, growth, mortality and morbidity compared to late initiation (during hospitalization and after hospital discharge) in low-weight NBs*	*The early skin-to-skin contact group had higher proportion of exclusive breastfeeding, higher breastfeeding rate during hospitalization, and a higher proportion of exclusive breastfeeding up to one month after hospital discharge, The incidence of apnea and recurrent apnea requiring ventilation was significantly reduced in the early skin-to-skin contact group, There was no significant difference in mortality, morbidity, and growth during hospitalization and after hospital discharge*
Nagai *et al.* [82]	*Randomized controlled clinical trial,*	*n = 73, Weight: < 2,500g, Age: < 24 hours, Relatively stable clinical conditions*	*Two groups: early skin-to-skin contact within the first 24 hours of life (n = 37)., Control: conventional care performed initially with skin contact after 48 - 72 hours of life (n = 36).*	*Evaluate the effectiveness of early skin contact initiation for relatively stable low-weight NBs in a resource-constrained country*	*There were no differences in the incidence of morbidity, Weight loss from birth up to 24 hours (and up to 48 hours) of life was significantly lower in the early skin-to-skin contact group compared with the control group, The occurrence of adverse effects and length of hospitalization did not differ between the groups*
Sharma *et al.* [83]	*Randomized controlled clinical trial*	*n = 141, Weight: < 1,100g, Clinically stable*	*Two groups: skin-to-skin contact (n = 71) and conventional care (n = 70) when NBs reached 1,150g.*	*Assess weight gain (g/day) from start of randomization to full-term (40 weeks), Variables studied: weight gain (g/day), Secondary outcomes: weight, length and head circumference at 40 weeks; intra-hospital weight gain (g/day), length (cm/week) and head circumference (cm/week) following randomization; breastfeeding rates at hospital discharge and at full-term age; neonatal ICU readmissions (level III or intermediate care unit)*	*Average weight gain, as well as weight, length and head circumference at term corrected age were comparable in both groups, There was a significant reduction in hospitalization time in the conventional care group and a significant increase in weight gain before discharge in the skin-to-skin contact group*

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Mitchell *et al.*[84]	*Randomized controlled clinical trial, ,*	*n = 38, GA: 27 - 30 weeks , Weight: < 1,311g , Receiving ventilatory support (MV, CPAP or nasal cannula)*	*Two groups: , Control Group (n = 19), Skin-to-Skin Contact Group (n = 19) ,*	*Determine if stress on PTNBs (measured by salivary cortisol levels) decreases after 5 days of skin-to-skin contact compared to 5 days in standard care, Determine if skin-to-skin provides sustained pain relief following the period of contact, Salivary cortisol was collected and evaluated on the 5th and 10th day of life, PIPP pain score was measured during routine tracheal and nasal aspiration because such procedures are considered painful,*	*Skin-to-skin contact did not affect basal salivary cortisol levels in PTNBs compared to standard care , Salivary cortisol levels decreased in both groups between the 5th and 10th day of life, demonstrating that the day of life variable should be considered when salivary cortisol is evaluated in PTNBs, Skin-to-skin contact did not affect PIPP scores after aspiration, as NBs were not in skin-to-skin contact during the procedure*
Ghavane *et al.*[85]	*Randomized controlled clinical trial*	*n = 140, Weight: < 1,500g, Hemodynamically stable; tolerating spoon feeding of 150mL/kg /day*	*Two groups: skin-to-skin contact (n = 71) and conventional care (n = 69)*	*Evaluate the effectiveness of early NB skin-to-skin contact in the Kangaroo unit compared to conventional care in the neonatal unit, in relation to the growth and breastfeeding of very low weight NBs at 40 weeks corrected age. , Variables studied: mean weight gain (g/kg/day) from randomization to corrected term age.*	*At full-term GA there were no differences between groups regarding mean weight gain (g/kg/day) after randomization and breastfeeding rate. , Skin-to-skin contact in the Kangaroo unit is as effective as conventional care at the neonatal unit with no increase in mortality or morbidity in very low weight NBs.*
Sharma *et al.*[86]	*Randomized controlled clinical trial*	*n = 141, GA: ≤ 32 weeks, Weight: < 1,000g, Clinically stable*	*Two groups: 71 KWC Group and 70 to Intermediate Intensive Care Group*	*Compare growth and cost-effectiveness of skin-to-skin contact with intermediate intensive care*	*Average weight gain, as well as weight, length and head circumference at term corrected age were comparable in both groups, Initiating early shifting to Kangaroo ward is cost effective intervention and have huge monetary implication in resource poor countries*

GA - gestational age; BW - birth weight; HR - heart rate; SpO_2 - oxygen saturation; FiO_2 - fraction of inspired oxygen; NB - newborn; CPAP - continuous positive airway pressure; $TcPCO_2$ - transcutaneous carbon dioxide pressure; SSC - skin-to-skin care ; NICU - neonatal intensive care unit; PTNB - preterm newborn; ETT - endotracheal tube; HFNC - high flow nasal cannula; rcO_2 : Regional cerebral oxygenation; HR - heart rate; cFTOE - cerebral fractional tissue oxygen extraction; AT - axillary temperature; RR - respiratory rate; FTNB - full-term newborn; KC - kangoroo care;; PIPP - Premature Infant Pain Profile; KWC - kangorro ward care.

Table 8S - Studies included for multisensory stimulation recommendations

Author	*Type of study*	*Sample*	*Interventions*	*Main outcomes*	*Main results*
Kanagabasai et al.[88]	*Randomized controlled*	*n = 50 , GA: 28 - 36 weeks , Weight: 1,000 to 2,000g*	*Two groups: Control Group (n = 25); Multisensory Stimulation Group (n = 25) submitted to interventions in five 12-minute sessions per week until hospital discharge*	*Neuromotor development evaluation*	*The multisensory intervention group had better muscle tone*
Medoff-Cooper et al.[89]	*Randomized controlled*	*n = 183, GA: 29 - 34 weeks , Weight: not disclosure*	*Two groups: Control Group (n = 93); Multisensory Stimulation (ATVV) Group (n =90) to evaluate sucking organization PTNBs following a multisensory stimulation, ATVV = 10' of auditory (female voice), tactile (moderate touch stroking or massage) and visual (eye to eye) stimulation, followed by 5' of vestibular stimulation (horizontal rocking)*	*Infant sucking was digitally recorded*	*ATVV infants exhibited improved sucking organization during hospitalization*
White-Traut et al.[90]	*Randomized controlled*	*n = 195 , GA = 29 to 34 weeks , Weight: not disclosure*	*Two groups: Control Group (n = 95), H-Hope Group (n = 90): ATVV protocol performed twice more maternal participatory guidance sessions by a nurse-community advocate team daily for 6 consecutive weeks*	*Behavioral state (frequency of oral behaviors and time of alertness)*	*The intervention group showed greater frequency of oral behaviors and increased alertness*
White-Traut et al.[91]	*Randomized controlled*	*n = 198 , GA: 29 to 34 weeks , Weight: not disclosure*	*Two groups: , Control Group (n = 102), H-Hope Group (n = 96)*	*Improved mother-baby interaction during feeding and play at 6-weeks corrected age*	*The intervention group had better mother-baby interaction*
White-Traut et al.[92]	*Randomized controlled*	*n = 182 , GA: 29 - 34 weeks , Average weight = 1,865g*	*Two groups: Control group (N = 94)., H-Hope Group (n = 88): ATVV protocol performed twice daily for 6 consecutive weeks*	*Weight-length growth measured by weight and height*	*The intervention group had faster weight-length gain than the control group*

GA- gestational age; ATVV- protocol Auditory, Tactile, Visual and Vestibular stimulus; PTNBs- preterm newborns; H-HOPE - Hospital to Home: Optimizing the Infant's Environment.

Table 9S - Studies included for multisensory skin-to-skin stimulation recommendations

Author	Type of study	Sample	Interventions	Main outcomes	Main results
Erdem et al.[95]	Randomized controlled	n = 28 , GA: 26 - 32 weeks , Weight: ≤ 1,000g	Two groups: , Control Group (n = 14) , Daily Mobilization Group (n = 14): Moyer-Mileur* protocol for 4 weeks (5 weekly sessions once a day)	Bone mineralization and anthropometric indices	The intervention group showed weight (p = 0.002) and height (p = 0.015) increase, as well as improved bone mineralization (p ≤ 0.001) compared to the control group
Tosun et al.[96]	Randomized controlled	n = 40 , GA: 26 - 32 weeks , Birth weight: 800 – 1,600g , Low-risk PTNBs	Two groups:, Control Group (n = 20), Intervention Group (n = 20): Moyer-Mileur protocol for 4 weeks (5 weekly sessions once a day)	Bone mineralization and anthropometric indices	The intervention group improved its bone mineralization (p ≤ 0.001) and anthropometric indices (p ≤ 0.001) compared to the control group
Vignochi et al.[97]	Randomized controlled	n = 30 , GA: ≤ 35 weeks , Weight: not disclosed	Two groups: , Control Group (n = 15); , Physiotherapy Group (n = 15): passive flexion-extension movements associated with mild joint compression/decompression for 15 minutes 5 times a week (until NB reaches 2,000g), Bone metabolism: imbalance between bone formation and resorption was lower in the intervention group	Bone metabolism	Imbalance between bone formation and resorption was lower in the intervention group
Litmanovitz et al.[98]	Randomized controlled	n = 34 PTNBs, GA: 28.6 ± 1.1 weeks, Weight: 1,217g ± 55g	3 Groups: , Group 1 Control (n = 10): no interventions, Group 2 (n = 13): mobilizations twice a day, Group 3 (n = 11): mobilizations once a day. Mobilization started at the NB's 08 ± 2.4 days of life and continued for 4 consecutive weeks, Mobilization protocols: passive mobilization consisting of flexion-extension of the extremities (upper and lower limbs)	Bone mineralization assessed by ultrasound	There was decreased bone loss in Group 2 compared to the other groups (p = 0.03), suggesting that passive mobilization performed twice a day may prevent demineralization
Chen et al.[99]	Randomized controlled clinical trial	n = 16 , GA: not disclosed, Birth weight: ≤ 1,500g	2 Groups, Control Group (n = 8): routine care , Intervention Group (n = 8): submitted to the Moyer-Mileur* protocol.	Bone mineralization assessed by ultrasound	There was an increase in bone mineralization in the intervention group compared to the control group

*GA- gestational age; PTNBs- preterm newborns; NB - newborn. * Moyer-Mileur* protocol.is: Extension and flexion in the range of motion exercise against extremity resistance, performed for wrists, elbows, shoulders, ankles, knees, and hip-joints (acetabulofemoral joints), 5 days/week for 4 weeks with one session a day. Each activity repeated 5 - 8 times.*