RESEARCH PAPER

ADD-ON Efficacy Of Oil Massage (*Abhyanga*) Along With Standard Neonatal Care In Neonatal Hyperbilirubinemia: Study Protocol For An Open-Label Randomised Controlled Trial

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ABSTRACT
Neonatal hyperbilirubinemia is among the commonest conditions of the first two weeks of life and a leading cause of neonatal re-hospitalisation; severe neonatal jaundice remains a substantial public health burden in low- and middle-income countries, where access to phototherapy is uneven.[1,2] Neonatal massage has been reported to accelerate bilirubin clearance and to reduce biochemical markers of stress, but massage with medicated oils as described in Ayurveda (*abhyanga*) has not been evaluated in a randomised trial in neonates. This protocol describes an open-label, parallel-group, two-arm randomised controlled trial with 1:1 allocation, to be conducted in the neonatal nursery of the Department of *Kaumarabhritya*, All India Institute of Ayurveda, New Delhi. A total of 140 neonates (70 per arm) of gestational age above 28 weeks and birth weight above 1500 g, with an Apgar score above 7 at one minute and not requiring respiratory or parenteral support, will be enrolled after written informed parental consent. The intervention arm will receive oil massage delivered by the Ayurveda Neonatal Massage Therapy Protocol, a 15-minute tactile–kinetic–tactile sequence, twice daily for seven days, using *Bala taila* on day 1 and *Arukaladi taila* from day 2, in addition to standard neonatal care; the comparator arm will receive standard neonatal care alone, including phototherapy at nomogram-defined thresholds. The primary outcome is total serum bilirubin. Secondary outcomes are salivary cortisol, axillary temperature, insulin-like growth factor-1, the reduced-to-oxidised glutathione ratio, malondialdehyde, transcutaneous bilirubin, stool frequency and symptomatic adverse reactions attributable to phototherapy. Participants are followed for 14 days. The bilirubin trajectory will be analysed by repeated-measures analysis of variance, with effect sizes and 95% confidence intervals reported. The trial evaluates a low-cost, equipment-free and culturally established adjunct to standard neonatal care in a setting where the burden of severe neonatal jaundice is high; its principal limitations are the impossibility of masking a tactile intervention, the absence of a sham-massage arm and single-centre recruitment. The protocol is reported in accordance with the SPIRIT 2013 statement.

Keywords: Neonatal hyperbilirubinemia, Infant massage, *Abhyanga*, Ayurveda, Randomised controlled trial, Salivary cortisol, Oxidative stress, Study protocol.
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.INTRODUCTION

Clinically apparent jaundice occurs in 60–80% of neonates and approximately 10% require phototherapy.[1] Frank pathological hyperbilirubinemia is uncommon, and progression to bilirubin encephalopathy rarer still, yet the population-level burden of severe neonatal jaundice remains considerable in low- and middle-income countries, reported at 244.1 per 10,000 live births overall, 251.3 per 10,000 in the South-East Asian region and 667.8 per 10,000 in the African region.[2] Kernicterus, acute and chronic bilirubin encephalopathy and bilirubin-induced neurological dysfunction constitute a spectrum of largely preventable and largely irreversible sequelae, and management options in the pathological form are confined to phototherapy, intravenous immunoglobulin and exchange transfusion.[3] Unmet need for phototherapy is concentrated in precisely those regions where incidence is highest,[1] which places a premium on interventions that are inexpensive, deliverable without specialised equipment and acceptable to families.

Insults sustained in the neonatal period are associated with chronic neurodevelopmental, cognitive and behavioural sequelae that seldom reverse completely.[4] Neonates are exposed to procedural, environmental and psychological stressors during the perinatal period and in the nursery; these act on the hypothalamic–pituitary–

adrenal axis, the autonomic nervous system, gene expression and the gut–brain axis,[5] have been associated with impeded cortical network formation,[6] and predict later internalising behaviour in children born very preterm.[7] Oxidative stress underlies several neonatal morbidities of prematurity,[8] and phototherapy itself has been identified as an inducer of oxidative stress.[9] An adjunct that addressed bilirubin load, stress reactivity and redox balance simultaneously would therefore have value beyond bilirubin reduction alone.

Infant massage is a well-studied intervention with a broad reported effect profile, including improved weight-gain velocity, reduced procedural pain, improved thermoregulation, reduced stress behaviours and enhanced mother–infant bonding.[10–12] In jaundiced neonates specifically, the Field massage therapy protocol reduced bilirubin concentrations and increased stool frequency among infants receiving phototherapy,[13] and a dose–response relationship has been described between massage duration and bilirubin reduction.[14] Not every protocol has shown a direct effect: Vimala massage increased defecation frequency without significantly altering bilirubin.[15] A meta-analysis reported significantly lower cortisol concentrations in massaged infants,[16] and five days of massage lowered stress behaviour scores in preterm neonates.[17]

Ayurveda prescribes daily oil massage (*abhyanga*) for pacification of *vata dosha* and describes benefits including improved skin health, sleep, nourishment and firmness of body; in neonates, oil bath (*seka*) and *abhyanga* are indicated to mitigate procedural pain and the stress of parturition.[18] Despite this textual grounding and routine clinical use, the neonatal practices of *Kaumarabhritya* remain largely unevaluated. Two classical formulations are relevant. *Arukaladi taila* (*Sahasrayogam, Taila Prakaranam/14*) is prepared by processing sesame oil with the expressed juices of *bhringaraja*, *amrita*, *durva*, *gojihva* and *indralata* together with a paste of *kadalikanda*, and is indicated for all types of *kamala* (jaundice);[19] it has not previously been evaluated in an interventional study. *Bala taila* (*Ashtanga Hridaya*, *Sharira Sthana* 2/47–52) is a *bala*-root-based polyherbal sesame oil indicated in disorders of the puerperium and of childhood,[18] and has been used clinically in benign prostatic hyperplasia[20] and chronic suppurative otitis media.[21]

The present trial therefore tests whether oil massage delivered as a standardised, reproducible protocol and added to standard neonatal care reduces total serum bilirubin in neonates, compared with standard neonatal care alone. Withholding standard care, including phototherapy at nomogram-defined thresholds, would be unethical; the add-on design answers the clinically relevant question at the cost of not isolating the standalone effect of the Ayurvedic intervention.

Objectives and hypotheses

The primary objective is to compare the add-on efficacy of oil massage with *Arukaladi taila*, delivered by the Ayurveda Neonatal Massage Therapy Protocol for 15 minutes with moderate pressure twice daily for up to seven days in addition to standard newborn care, against standard newborn care alone, in reducing total serum bilirubin. Secondary objectives are to evaluate the add-on effect of oil massage on perinatal stress indexed by salivary cortisol, on thermoregulation indexed by mean body temperature, on serum insulin-like growth factor-1 (IGF-1), on antioxidant status indexed by the reduced/oxidised glutathione (GSH/GSSG) ratio and malondialdehyde (MDA), and on symptomatic adverse reactions attributable to phototherapy.

The null hypothesis is that oil massage with *Arukaladi taila*, delivered as specified in addition to standard newborn care, is equally or less efficacious than standard newborn care alone in reducing total serum bilirubin; the alternative hypothesis is that it is more efficacious.

MATERIALS AND METHODS

The protocol is reported in accordance with the SPIRIT 2013 statement.[22] The participant flow and timeline are shown in Figure 1 and the schedule of enrolment, interventions and assessments in Figure 2.

Trial design and setting

This is an open-label, parallel-group, randomised, controlled superiority trial with two arms and 1:1 allocation. The intervention period is seven days and follow-up a further seven days, giving a participant duration of 14 days. No interim analysis is planned. The trial will be conducted in the neonatal nursery of the Department of *Kaumarabhritya*, Hospital Block, All India Institute of Ayurveda, Sarita Vihar, New Delhi, an autonomous institution under the Ministry of AYUSH, Government of India. This is a single-centre trial.

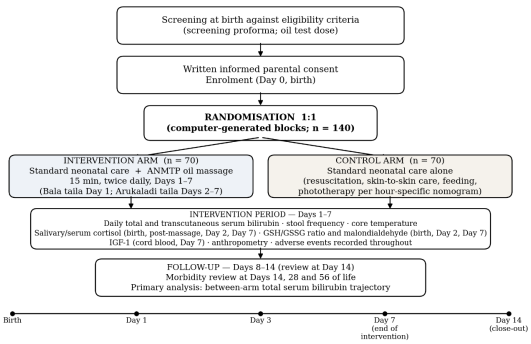

Figure 1: Participant flow and timeline. ANMTP, Ayurveda Neonatal Massage Therapy Protocol; GSH/GSSG, reduced/oxidised glutathione ratio; IGF-1, insulin-like growth factor-1.

Eligibility criteria

Inclusion criteria are: clinically stable neonates enrolled at birth, irrespective of sex and ethnicity; gestational age above 28 completed weeks and birth weight above 1500 g; Apgar score above 7 at one minute; no requirement for oxygen support, positive-pressure ventilation or parenteral nutrition; and written informed consent from a parent or legal guardian. Enrolment occurs at birth so that cord samples and the whole bilirubin trajectory are captured; neonates who develop hyperbilirubinemia meeting the ICD-11 KA87 definition during observation contribute to the primary analysis.

Exclusion criteria are: gestational age of 28 weeks or less; birth weight of 1500 g or less; rhesus or ABO incompatibility or glucose-6-phosphate dehydrogenase deficiency; birth injury; congenital anomaly; signs of infection or of intraventricular or subgaleal haemorrhage; signs of gastrointestinal obstruction or biliary atresia; requirement for oxygen support, positive-pressure ventilation, parenteral nutrition or other intravenous infusion; hypersensitivity to the oil test dose; both parents being minors; and maternal administration, before or after parturition, of narcotic agents, barbiturates, aspirin, chloral hydrate, reserpine or phenytoin sodium.

Neonatal hyperbilirubinemia is defined as total serum bilirubin above the 95th percentile for age in hours on the hour-specific bilirubin nomogram, and severe hyperbilirubinemia by onset before 24 hours of age or by jaundice requiring phototherapy.[3] Visual assessment by the Kramer dermal zone score is recorded as supplementary evidence only and is not used for treatment decisions.

Participants will be withdrawn if total serum bilirubin reaches 20 mg/dL or more; if features suggestive of bilirubin encephalopathy appear or exchange transfusion becomes indicated; on development of fever, sepsis, respiratory distress, necrotising enterocolitis, seizure, neurological dysfunction or other intercurrent illness; at parental request; or if the mother receives any drug listed in the exclusion criteria. Withdrawn participants continue to receive standard care and the reason for withdrawal is recorded.

Intervention

Oil massage will be delivered according to the Ayurveda Neonatal Massage Therapy Protocol (ANMTP), an adaptation of the Field massage therapy protocol, for 15 minutes per session, twice daily (morning and evening) for seven days. The first session begins no earlier than one hour after the first feed, to reduce the risk of vomiting. The first session uses *Bala taila*; from day 2 onwards *Arukaladi taila* is used. Both oils will be procured from manufacturers certified for good manufacturing practice, prepared according to the classical references cited above, and subjected to pharmacopoeial physicochemical quality control before use, with batch numbers recorded. Before first use of each oil, hypersensitivity is excluded by applying a test dose of three drops to the neonate's skin and observing for 30 minutes.

The therapist warms the hands to the neonate's body temperature and holds the neonate in cupped hands in a resting position, denoting permission-seeking. The hands are then oiled, the quantity being adjusted to body surface area and skin texture. Each session comprises three consecutive five-minute phases in the sequence tactile–kinetic–tactile. All strokes are performed supine; the prone position is avoided, being contraindicated in Ayurvedic massage technique because of pressure over the cardiac region. Pressure is standardised as moderate tactile pressure applied with the finger pulps, following the *Varmam* convention of approximately one-quarter *matra*. Reverse strokes are performed at reduced pressure, the direction of massage in Ayurveda being unidirectional (*anuloma*). Residual oil is wiped off with clean cotton after the session. Stroke counts are given in Table 1.

Table 1: Ayurveda Neonatal Massage Therapy Protocol — stroke sequence.

Phase	Segment and motion	Moves	Time per move
Tactile (supine)	Head downwards and reverse	12	5 s
Tactile (supine)	Neck to shoulders and reverse	12	5 s
Tactile (supine)	Upper back to waist and reverse	12	5 s
Tactile (supine)	Thighs to ankles and reverse	12	5 s
Tactile (supine)	Shoulders to wrists and reverse	12	5 s
Kinetic (supine)	Right arm	6	10 s
Kinetic (supine)	Left arm	6	10 s
Kinetic (supine)	Right leg	6	10 s
Kinetic (supine)	Left leg	6	10 s
Kinetic (supine)	Both legs	6	10 s

The third phase repeats the sequence of the first tactile phase.

Comparator and concomitant care

Both arms receive standard neonatal care. At delivery all neonates are resuscitated according to national neonatal resuscitation guidance; skin-to-skin care and breastfeeding, or the alternative feeding mode appropriate to gestational age, are initiated after resuscitation. In the control arm, skin-to-skin care is the contact exposure against which

post-massage salivary cortisol is compared. Phototherapy is provided to jaundiced neonates in both arms using a portable LED infant phototherapy device (Bird Meditech, model BM/LED/04; irradiance 35 μW/cm²/nm; emission peak as per manufacturer specification), the mode of administration being determined by the hour-specific bilirubin nomogram with reference to gestational age, birth weight and risk factors;[3] eyes and genitalia are shielded throughout. No oral Ayurvedic medication is administered. No restriction is placed on medically indicated treatment in either arm, and all concomitant medication is recorded. The trial is conducted on an inpatient basis and each session is entered on a compliance checklist within the case record form, recording the oil used and the reason for any session not delivered. Massage is suspended for any participant meeting a withdrawal criterion, on development of a local reaction to the oil, or at parental request, standard care continuing unchanged.

Outcomes

The primary outcome is total serum bilirubin (mg/dL), measured by point-of-care bilirubinometry on a heel-prick sample daily from birth until discharge or until the value falls below the phototherapy threshold for the day of life and gestational age; the primary comparison is the between-arm difference in bilirubin trajectory over the intervention period. Total serum bilirubin is the criterion on which diagnosis, escalation and de-escalation of treatment rest and is therefore the appropriate primary endpoint.[3]

Secondary outcomes are: salivary cortisol, a validated and minimally invasive index of neonatal stress,[23] measured at birth, immediately after massage (or after skin-to-skin care in controls), on day 2 and at discharge; axillary temperature; serum IGF-1, which predicts subsequent weight gain and linear growth[24] and is a postulated mediator of the growth effects of massage,[25] measured in cord blood and before discharge; the GSH/GSSG ratio and MDA, standard indices of intracellular redox status and of lipid peroxidation in the neonatal period,[26,27] measured at birth, on day 2 and at discharge, subject to feasibility and ethics approval; transcutaneous bilirubin, measured before massage on days 1 to 5 from the forehead and two sternal points, three readings at each point averaged; stool frequency, from a parent-maintained log; and symptomatic adverse reactions attributable to phototherapy. Anthropometry (weight, length, head, chest and mid-arm circumference) is recorded at birth and at discharge. The primary endpoint is the fall in total serum bilirubin below the phototherapy threshold for day of life and gestational age; secondary endpoints are a reduction in salivary cortisol, stabilisation of body temperature, a reduction in MDA, and increases in IGF-1 and the GSH/GSSG ratio.

	TIMEPOINT							
	Birth (0 h)	Alloc-ation	Post-massage Day 1	Day 1	Day 2	Day 3 and all. days	Day 7	Day 14 close-out
ENROLMENT								
Eligibility screen	●							
Informed consent	●							
Oil hypersensitivity test dose	●							
Randomisation (allocation)		●						
INTERVENTIONS								
ANMTP oil massage (intervention arm)			●	●	●	●	●	
Standard neonatal care (both arms)	●	●	●	●	●	●	●	
ASSESSMENTS								
Baseline and clinical variables	●							
Total serum bilirubin	●			●	●	●	●	
Transcutaneous bilirubin	●			●	●	●		
Salivary/serum cortisol	●		●		●		●	
Stool frequency	●			●	●	●	●	
GSH/GSSG ratio and malondialdehyde	●				●		●	
Insulin-like growth factor-1	●						●	
Core temperature					●	●	●	
Anthropometry	●						●	
Adverse events	●	●	●	●	●	●	●	●
Morbidity review (Days 14, 28, 56)								●

Figure 2: Schedule of enrolment, interventions and assessments (SPIRIT figure). Filled circles indicate the timepoints at which each procedure is performed.

Sample size

The sample size was calculated for the primary outcome using the standard formula for the comparison of two independent means, $N = 2 \times [(z_{1-\alpha/2} + z_{1-\beta})/\delta]^2 \times s^2$, with the parameters in Table 2, giving 70 participants per arm and 140 in total.

Table 2: Sample size parameters.

Parameter	Value
Mean reduction, test treatment	4.7 mg/dL
Mean reduction, standard treatment	3.7 mg/dL
Expected mean difference	1.0 mg/dL
Standard deviation (s)	2.012
Significance level, $z_{1-\alpha/2}$ (two-sided $\alpha = 0.05$)	1.96
Power, $z_{1-\beta}$ (80%)	0.84
Effect size (δ)	0.497
Computed sample size per group	63.47
Adjusted for 10% attrition	70 per group
Total sample size	140

Recruitment, randomisation and blinding

Consecutive neonates delivered at or admitted to the institutional nursery will be screened against the eligibility criteria using the screening proforma; mothers attending the institutional antenatal clinic will be counselled about the trial before delivery so that consent can be sought unhurriedly. Recruitment continues until 140 participants are enrolled. A computer-generated allocation sequence will be produced by block randomisation with equal block size, stratified to preserve balance across the sampling strata. Because the design is open-label

and enrolment occurs at birth, concealment rests on custody of the randomisation list: the sequence is generated by a person not involved in recruitment and held centrally, and each allocation is released only after eligibility has been confirmed and consent obtained. The investigator enrols participants and requests the next allocation from the sequence holder. Neither caregivers, therapists nor clinical outcome assessors can be masked to a tactile intervention delivered by the investigator. Laboratory analyses of cortisol, IGF-1, GSH/GSSG and MDA will be performed on coded samples by personnel unaware of allocation, and statistical analysis will be conducted on a coded dataset.

Data collection and management

Data are recorded on custom case record forms comprising a screening proforma, an antenatal and delivery record, a birth note, a structured newborn physical examination, the assessment grid and the compliance checklist. Saliva is collected without salivation-stimulating agents using polyvinyl alcohol-based cellulose ophthalmic sponge spears; maternal dietary confounders are avoided for one hour before sampling and the neonate's mouth is wiped before collection, although feeding cannot be withheld because of the risk of hypoglycaemia. The sponge is placed sublingually for three to five minutes until visibly saturated, transferred to a 5 mL polypropylene cuvette, covered and centrifuged at 6000 rpm for 15 minutes, and the supernatant stored at −20 °C until assay; cortisol is determined in duplicate (25 µL per determination) by enzyme-linked immunosorbent assay with a stated specificity of 1.0 ng/mL.[23] IGF-1 is measured by enzyme-linked immunosorbent assay with a detection limit of 0.025 ng/mL. Blood is drawn in accordance with World Health Organization phlebotomy guidance for children and neonates,[28] and cumulative sample volume remains within accepted safe limits of 1–5% of total blood volume,[29] the trial observing a 3% ceiling.[30] Cord blood is used wherever a birth sample is required, avoiding an additional venepuncture. Data are captured in Epi Info 7.2.5 using custom forms and retained for at least five years; participants are identified in the database by code only, paper forms are held in a locked cabinet and the electronic dataset on a password-protected institutional machine with restricted access. Because the intervention and most assessments occur during a single inpatient episode, loss to follow-up is expected to be low; contact details recorded at enrolment are used to arrange the day-14 review.

Statistical methods

Efficacy will be analysed in the per-protocol set and safety in the intention-to-treat set; participants withdrawn from the trial will be summarised separately and by reason for withdrawal. Demographic and baseline characteristics will be summarised by arm, continuous variables as n, mean, standard deviation, standard error, median, minimum and maximum, and categorical variables as counts and percentages. Because all principal outcomes are continuous, measured in two groups and assessed at multiple timepoints, the primary analysis of total serum bilirubin will use repeated-measures analysis of variance with arm as the between-participant factor, time as the within-participant factor and the arm × time interaction as the term of interest. Normality will be assessed by the Shapiro–Wilk test, and Friedman's test used where the assumption fails. Within-group before-and-after differences will be examined by the paired t test or the Wilcoxon signed-rank test, and between-group differences at individual timepoints by the unpaired t test or the Mann–Whitney U test, as the distribution dictates. Standardised effect sizes with 95% confidence intervals will be reported alongside p values for all principal comparisons, and a two-sided p value of 0.05 or less taken as statistically significant. Analyses will be performed in IBM SPSS Statistics for Windows, version 26. The extent and pattern of missing data will be reported; no imputation is planned for the per-protocol analysis and sensitivity to missingness will be examined descriptively. No confirmatory subgroup analysis is planned, and description by gestational-age stratum will be reported as hypothesis-generating only.

Three sources of confounding are anticipated. Investigations are themselves stressors, so sample collections are consolidated into a single daily timepoint to minimise handling; maternal diet and medication influence the onset, peak and duration of jaundice, and will be minimised and recorded; and coping capacity for jaundice, stress and thermal instability differs between preterm and term neonates, which stratified randomisation is intended to balance across arms.

Data monitoring, harms and auditing

Given the short duration, the low-risk nature of the intervention and the absence of a planned interim analysis, a formal independent data monitoring committee has not been constituted; safety oversight rests with the guide, co-guide and institutional neonatologist, with recourse to the Institutional Ethics Committee. Solicited harms include local skin reaction to the oil, hypothermia during a session, feeding intolerance or vomiting, and desaturation or bradycardia during handling. All adverse events are recorded with onset, severity, action taken and outcome; suspected adverse drug reactions are reported on the National Pharmacovigilance Programme for ASU&H Drugs form to the AYUSH Suraksha portal within 24 hours, with a detailed report within one week, and causality assessed by the Naranjo probability scale. Management of adverse events is undertaken in consultation with the institutional neonatologist. Trial conduct is subject to audit by the Institutional Ethics Committee and by the university, independently of the investigators.

Ethical considerations

The protocol, participant information sheet and consent form were reviewed by the Institutional Review Board of the All India Institute of Ayurveda and revised in accordance with its observations; the revised documents were submitted to the Institutional Ethics Committee for PhD studies. Recruitment will not begin until written ethics clearance is issued [approval number and date] and the trial has been registered with the Clinical Trials Registry – India. The trial will be conducted in accordance with the Declaration of Helsinki, the Indian Council of Medical Research national ethical guidelines, AYUSH and World Health Organization guidance, and the special considerations applicable to research involving neonates; both investigational oils are formulations described in books listed in Schedule I of the Drugs and Cosmetics Act, 1940. Written informed consent is obtained from a parent or legal guardian before any trial procedure, separately for participation and for the use of biological samples, and where the parent cannot read the consent is witnessed by an impartial witness. Substantive amendments will be submitted to the Institutional Ethics Committee before implementation and reflected in the registry record and in any publication. Continued clinical care after the trial period is provided on the basis of total and conjugated serum bilirubin values and the neonate's condition; intercurrent illness during the trial is treated and all trial investigations performed at no cost to the family, and no financial compensation is offered for participation.

RESULTS

The trial had not commenced recruitment at the time of writing; this report presents the pre-specified protocol and no participant data. The synopsis was reviewed by the Institutional Review Board, revised in response to its observations, which concerned the addition of a secondary objective on adverse reactions attributable to standard neonatal care and a more realistic sample size, and submitted to the Institutional Ethics Committee. Recruitment of 140 neonates is anticipated within the course tenure, with the primary analysis conducted once the last enrolled participant has completed the day-14 review.

Reporting of results will follow the CONSORT 2010 statement and its extension for non-pharmacological treatments,[31] and will comprise a participant flow diagram; a table of baseline characteristics by arm; the primary analysis of the total serum bilirubin trajectory with the arm × time interaction, effect size and 95% confidence interval; corresponding analyses of salivary cortisol, temperature, IGF-1, GSH/GSSG ratio, MDA, transcutaneous bilirubin and stool frequency; the proportion of participants in each arm requiring phototherapy and the duration of phototherapy; and a full account of adverse events by arm. Results will be submitted for publication irrespective of the direction of the findings, and the registry record updated accordingly.

DISCUSSION

Neonatal massage is inexpensive, requires no equipment, is culturally established across South Asia and is already delivered by caregivers in many households; if it accelerates bilirubin clearance to a clinically meaningful degree, it is among the more readily scalable adjuncts available where phototherapy capacity is limited. The existing evidence is suggestive but heterogeneous, protocols differing in duration, frequency, technique and medium, and the trials conducted to date have generally been small.[13–15] This trial contributes a fully specified and reproducible massage protocol; the first controlled evaluation of *Arukaladi taila*, a classically indicated anti-icteric formulation never before tested in an interventional study; and a panel of stress and redox markers alongside the bilirubin endpoint, which permits a mechanistic reading of any effect observed rather than an efficacy signal alone.

The design has several strengths. The intervention is standardised to the level of stroke count, pressure and phase duration, which is unusual in the massage literature and should aid replication. Enrolment at birth captures the whole bilirubin trajectory rather than a segment of it. The outcome panel spans the clinically decisive endpoint, a validated stress marker, a growth mediator and two redox markers, and the assessment schedule has been consolidated so as to add as little handling as possible to routine care.

Several limitations should be acknowledged. The trial is open-label, since a tactile intervention cannot be masked, and the absence of a sham-massage arm means that the specific contribution of the medicated oils cannot be separated from that of touch and handling; an oil-free comparator was judged to confound the mechanical and pharmacological components rather than to separate them. The standalone effect of the Ayurvedic intervention cannot be established, because withholding standard neonatal care would be unethical. Oral interventions, which are the mainstay of jaundice management in Ayurveda, are not tested, given the vulnerability of neonates to oral drug toxicity and the absence of neonatal safety data. Recruitment spans a wide gestational range rather than being confined to the groups at highest risk, because preterm delivery is infrequent at the study site, which limits power for the preterm subgroup. Finally, this is a single-centre trial, which constrains generalisability, and the assessment schedule itself imposes handling on the neonate, affecting both arms.

If the trial is positive, its translational value would lie in supporting the incorporation of medicated oil massage into neonatal care pathways, in providing preliminary leads for oral Ayurvedic interventions in

neonatal jaundice, in generating a repository of Ayurvedic neonatal care practice, and in informing the development of standardised neonatal care products. If it is negative, it will nonetheless establish a reproducible protocol and a biomarker panel against which subsequent studies of neonatal massage in this population can be designed.

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REFERENCES

1. Bhutani VK. Editorial: building evidence to manage newborn jaundice worldwide. Indian J Pediatr. 2012;79(2):253-5.
2. Slusher TM, Zamora TG, Appiah D, Stanke JU, Strand MA, Lee BW, et al. Burden of severe neonatal jaundice: a systematic review and meta-analysis. BMJ Paediatr Open. 2017;1(1):e000105.
3. Eichenwald EC, Hansen AR, Martin CR, Stark AR, editors. Cloherty and Stark's manual of neonatal care. 8th ed. Philadelphia: Wolters Kluwer; 2017.
4. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet. 2012;379(9814):445-52.
5. Nist MD, Harrison TM, Steward DK. The biological embedding of neonatal stress exposure: a conceptual model describing the mechanisms of stress-induced neurodevelopmental impairment in preterm infants. Res Nurs Health. 2019;42(1):61-71.
6. van Dokkum NH, de Kroon MLA, Reijneveld SA, Bos AF. Neonatal stress, health, and development in preterms: a systematic review. Pediatrics. 2021;148(4):e2021050414.
7. McLean MA, Scoten OC, Chau CMY, Synnes A, Miller SP, Grunau RE. Association of neonatal pain-related stress and parent interaction with internalizing behaviors across 1.5, 3.0, 4.5, and 8.0 years in children born very preterm. JAMA Netw Open. 2022;5(11):e2238088.
8. Shoji H, Koletzko B. Oxidative stress and antioxidant protection in the perinatal period. Curr Opin Clin Nutr Metab Care. 2007;10(3):324-8.
9. Shekeeb Shahab M, Kumar P, Sharma N, Narang A, Prasad R. Evaluation of oxidant and antioxidant status in term neonates: a plausible protective role of bilirubin. Mol Cell Biochem. 2008;317(1-2):51-9.
10. Field T. Pediatric massage therapy research: a narrative review. Children. 2019;6(6):78.
11. Mrljak R, Arnsteg Danielsson A, Hedov G, Garmy P. Effects of infant massage: a systematic review. Int J Environ Res Public Health. 2022;19(11):6378.
12. Pados BF, McGlothen-Bell K. Benefits of infant massage for infants and parents in the NICU. Nurs Womens Health. 2019;23(3):265-71.
13. Lin CH, Yang HC, Cheng CS, Yen CE. Effects of infant massage on jaundiced neonates undergoing phototherapy. Ital J Pediatr. 2015;41:94.
14. Shahbazi M, Khazaei S, Moslehi S, Shahbazi F. Effect of massage therapy for the treatment of neonatal jaundice: a systematic review and dose-response meta-analysis. Int J Pediatr. 2022;2022:9161074.
15. Seyyedrasooli A, Valizadeh L, Hosseini MB, Asgari Jafarabadi M, Mohammadzad M. Effect of Vimala massage on physiological jaundice in infants: a randomized controlled trial. J Caring Sci. 2014;3(3):165-73.
16. Jabraeili M, Mirghafourvand M, Montazeri M, Rahkar Farshi M. The effect of massage on cortisol level in infants: a systematic review and meta-analysis. J Neonatal Nurs. 2023;29(5):715-23.
17. Hernandez-Reif M, Diego M, Field T. Preterm infants show reduced stress behaviors and activity after 5 days of massage therapy. Infant Behav Dev. 2007;30(4):557-61.
18. Vagbhata. *Ashtangahridaya*, with the commentaries *Sarvangasundara* of Arunadatta and *Ayurvedarasayana* of Hemadri. Vol. 1. 6th ed. Mumbai: Nirnaya-Sagar Press; 1939.
19. Anonymous. *Sahasrayogam* with *Sujanapriya* commentary. Alappuzha: Vidyarambham Press; 2012.
20. Banothe GD, Mahanta V, Gupta SK, Dudhamal TS. A clinical evaluation of *Kanchanara Guggulu* and *Bala Taila Matra Basti* in the management of *Mutraghata* with special reference to benign prostatic hyperplasia. Ayu. 2018;39(2):65-71.
21. Negi D, Bishwal R, Aditi. Role of *Bala Taila Nasya* and *Rasnadi Guggulu* in *Karnasrava* (chronic suppurative otitis media). Int J Ayurveda Pharma Res. 2022;10(1):8-13.
22. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-7.
23. Cabral DM, Antonini SRR, Custodio RJ, Martinelli CE Jr, Da Silva CAB. Measurement of salivary cortisol as a marker of stress in newborns in a neonatal intensive care unit. Horm Res Paediatr. 2013;79(6):373-8.
24. Lo HC, Tsao LY, Hsu WY, Chen HN, Yu WK, Chi CY. Relation of cord serum levels of growth hormone, insulin-like growth factors, insulin-like growth factor binding proteins, leptin, and interleukin-6 with birth weight, birth length, and head circumference in term and preterm neonates. Nutrition. 2002;18(7-8):604-8.
25. Field T, Diego M, Hernandez-Reif M, Dieter JNI, Kumar AM, Schanberg S, et al. Insulin and

insulin-like growth factor 1 (IGF-1) increased in preterm neonates following massage therapy. J Dev Behav Pediatr. 2008;29(6):463-6.
26. Millan I, Pinero-Ramos JD, Lara I, Parra-Llorca A, Torres-Cuevas I, Vento M. Oxidative stress in the newborn period: useful biomarkers in the clinical setting. Antioxidants. 2018;7(12):193.
27. Rook D, te Braake FWJ, Schierbeek H, Longini M, Buonocore G, van Goudoever JB. Glutathione synthesis rates in early postnatal life. Pediatr Res. 2010;67(4):407-11.
28. World Health Organization. Paediatric and neonatal blood sampling. In: WHO guidelines on drawing blood: best practices in phlebotomy. Geneva: World Health Organization; 2010. p. 51-9.
29. Howie SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011;89(1):46-53.
30. Peplow C, Assfalg R, Beyerlein A, Hasford J, Bonifacio E, Ziegler AG. Blood draws up to 3% of blood volume in clinical trials are safe in children. Acta Paediatr. 2019;108(5):940-4.
31. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P; CONSORT NPT Group. CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. Ann Intern Med. 2017;167(1):40-7.