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# Intermittent phototherapy versus continuous phototherapy for neonatal jaundice (Review)

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[Intervention Review]

# Intermittent phototherapy versus continuous phototherapy for neonatal jaundice

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## ABSTRACT

### Background

Phototherapy is a widely accepted, effective first-line therapy for neonatal jaundice. It is traditionally used continuously but intermittent phototherapy has been proposed as an equally effective alternative with practical advantages of improved maternal feeding and bonding. The effectiveness of intermittent phototherapy compared with continuous phototherapy is unknown.

### Objectives

To assess the safety and effectiveness of intermittent phototherapy compared with continuous phototherapy.

### Search methods

Searches were conducted on 31 January 2022 in the following databases: CENTRAL via CRS Web, MEDLINE and Embase via Ovid. We also searched clinical trials databases and the reference lists of retrieved articles for randomised controlled trials (RCTs) and quasi-randomised trials.

### Selection criteria

We included RCTs, cluster-RCTs and quasi-RCTs comparing intermittent phototherapy with continuous phototherapy in jaundiced infants (both term and preterm) up to the age of 30 days. We compared intermittent phototherapy with continuous phototherapy by any method and at any dose and duration as defined by the authors.

### Data collection and analysis

Three review authors independently selected trials, assessed trial quality and extracted data from included studies. We performed fixed-effect analyses and expressed treatment effects as mean difference (MD), risk ratio (RR) and risk difference (RD) with 95% confidence intervals (CIs). Our primary outcomes of interest were rate of decline of serum bilirubin, and kernicterus. We used the GRADE approach to assess the certainty of evidence.

### Main results

We included 12 RCTs (1600 infants) in the review. There is one ongoing study and four awaiting classification. There was little or no difference between intermittent phototherapy and continuous phototherapy with respect to rate of decline of bilirubin in jaundiced newborn infants (MD -0.09 micromol/L/hr, 95% CI -0.21 to 0.03; $I^2$ = 61%; 10 studies; 1225 infants; low-certainty evidence). One study involving 60 infants reported no incidence of bilirubin induced brain dysfunction (BIND). It is uncertain whether either intermittent or continuous phototherapy reduces BIND because the certainty of this evidence is very low. There was little or no difference in treatment

failure (RD 0.03, 95% CI 0.08 to 0.15; RR 1.63, 95% CI 0.29 to 9.17; 1 study; 75 infants; very low-certainty evidence) or infant mortality (RD -0.01, 95% CI -0.03 to 0.01; RR 0.69, 95% CI 0.37 to 1.31 $I^2$ = 0%; 10 studies, 1470 infants; low-certainty evidence).

**Authors' conclusions**

The available evidence detected little or no difference between intermittent and continuous phototherapy with respect to rate of decline of bilirubin. Continuous phototherapy appears to be more effective in preterm infants, however, the risks of continuous phototherapy and the potential benefits of a slightly lower bilirubin level are unknown. Intermittent phototherapy is associated with a decrease in the total number of hours of phototherapy exposure. There are theoretical benefits to intermittent regimens but there are important safety outcomes that were inadequately addressed. Large, well designed, prospective trials are needed in both preterm and term infants before it can be concluded that intermittent and continuous phototherapy regimens are equally effective.

## PLAIN LANGUAGE SUMMARY

**Intermittent phototherapy versus continuous phototherapy for neonatal jaundice**

**Review question**

In jaundiced newborn infants, is intermittent phototherapy compared with continuous phototherapy effective in reducing bilirubin levels.

**Background**

Neonatal jaundice is a yellowish discolouration of the of the newborn infant's skin due to high bilirubin (a yellow compound that occurs naturally in the blood) levels. Phototherapy (light therapy) is widely accepted as an effective treatment for jaundiced newborn infants. Phototherapy is usually used continuously but intermittent phototherapy has some potential advantages such as improved maternal feeding and bonding. We do not know if intermittent phototherapy is as effective as continuous phototherapy.

**Study characteristics**

We found 33 studies that assessed the effect of intermittent phototherapy in infants through searches of medical databases up to January 2022. Of these, 12 studies (involving a total of 1600 infants) were eligible for inclusion in this review. One study is currently ongoing and four are awaiting classification. Our primary outcomes of interest were the rate of fall in the serum bilirubin levels and bilirubin-induced brain dysfunction (BIND). Search is up-to-date as of 31 January 2022.

**Key results**

We found little or no difference between intermittent phototherapy and continuous phototherapy in reducing bilirubin levels. Continuous phototherapy was more effective in preterm infants, however, we do not know if this is a meaningful difference. Intermittent phototherapy is associated with a decrease in the total number of hours of phototherapy exposure. There are theoretical benefits to intermittent regimens but there are important safety outcomes that were inadequately addressed.

**Certainty of evidence**

Overall, we rated the certainty of evidence as low or very low. Large, high-quality trials are needed in both preterm and term infants before it can be concluded that intermittent and continuous phototherapy regimens are equally effective.

## SUMMARY OF FINDINGS

### Summary of findings 1. Intermittent phototherapy compared to continuous phototherapy for neonatal jaundice

**Intermittent phototherapy compared to continuous phototherapy for neonatal jaundice**

**Patient or population:** neonatal jaundice
**Setting:** newborn care
**Intervention:** intermittent phototherapy
**Comparison:** continuous phototherapy

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with continuous phototherapy | Risk with intermittent phototherapy | | | | |
| Rate of decline of serum bilirubin (micromol/L/hr) | The mean rate of decline of serum bilirubin (micromol/L/hr) was 1.601 micromol/L/h | MD 0.09 micromol/L/h lower (0.21 lower to 0.03 higher) | - | 1225 (10 RCTs) | ⊕⊕⊖⊖ LOW [1 2] | |
| Bilirubin-induced brain dysfunction (defined as either the pathological finding of deep-yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei or acute or chronic neurological deficit including athetoid cerebral palsy, impaired upward gaze and deafness or isolated conditions, such as auditory neuropathy or dyssynchrony) | Study population | | not estimable | 60 (1 RCT) | ⊕⊖⊖⊖ VERY LOW [3 4] | |
| | 0 per 1000 | 0 per 1000 (0 to 0) | | | | |
| Treatment failure (need to restart phototherapy or exchange transfusion or both) | Study population | | not estimable | 75 (1 RCT) | ⊕⊖⊖⊖ VERY LOW [3 5] | |
| | 51 per 1000 | 0 per 1000 (0 to 0) | | | | |
| Mortality (all cause) | Study population | | not estimable | 1470 (10 RCTs) | ⊕⊕⊖⊖ LOW [6] | |
| | 28 per 1000 | 0 per 1000 (0 to 0) | | | | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Moderate heterogeneity
[2] Optimal information size not met
[3] Reported by single study
[4] No events reported in a single study
[5] Effect size includes both appreciable benefit and appreciable harm.
[6] Optimal information size not met. Effect size includes both appreciable benefit and appreciable harm.

# BACKGROUND

## Description of the condition

Jaundice is the yellow discolouration of the skin caused by the presence of bilirubin in the soft tissues and can result from high levels of conjugated or unconjugated bilirubin. About 97% of full-term and preterm neonates demonstrate a biochemical hyperbilirubinaemia (serum bilirubin level > 1 mg/dL) and about 65% appear clinically jaundiced (serum bilirubin > 5 mg/dL) (Keren 2008; Maisels 1986). Physiological jaundice results from a high level of circulating unconjugated bilirubin due to accelerated red cell break-down, reduced liver bilirubin handling capacity and increased enterohepatic circulation (Horn 2006). Pathologic jaundice results from conditions such as haemolytic disease of the newborn, sepsis, and inborn errors of metabolism (Maisels 2005). Supplementary feeding, percentage weight loss, ABO incompatibility and vacuum extraction significantly increase the risk of jaundice (Bertini 2001).

Untreated indirect hyperbilirubinaemia may result in bilirubin-induced brain dysfunction (BIND). In the acute phase, the signs of BIND are poor feeding, lethargy, high-pitched cry, hypertonia or hypotonia, opisthotonos and seizures. The chronic manifestations of BIND include athetoid cerebral palsy, motor delay, gaze palsy, dental dysplasia, mental retardation and sensorineural hearing loss. When neurological signs are evident in the infant, permanent damage has already occurred, leading to death or long-term disability (AAP 2004).

## Description of the intervention

In 1985, the National Institute of Child Health and Human Development (NICHHD) reported that phototherapy was as effective as exchange transfusion in preventing neurological sequelae (NICHHD 1985). Since then, phototherapy has been widely adopted as the initial therapy of choice for neonatal jaundice (Eberhard 1994; Knudsen 1991). Phototherapy converts the bilirubin through structural photoisomerisation and photo-oxidation into excretable products. This molecular conversion occurs when bilirubin accumulating in the skin is exposed to light of wave-lengths 425 to 475 nm (blue-green spectrum). The effectiveness of phototherapy is related to the area of skin exposed, the radiant energy, the sources and wave-length of the light (Tan 1982; Thaithumyanon 2002), and the cause and severity of jaundice (Maisels 2008). The guidelines or protocols used to determine the need for phototherapy may vary from one study to the other. Lewis and colleagues showed that early institution of phototherapy produced a more rapid decline in serum bilirubin levels compared to delayed phototherapy (Lewis 1982). Side effects of phototherapy include temperature instability manifesting as either hyperthermia or hypothermia, dehydration (Oh 1972), gastrointestinal hypermotility, diarrhoea, drowsiness, and exanthemata (Knudsen 1991). Phototherapy has been linked to persistent ductus arteriosus (Clyman 1978; Rosenfeld 1986; Travadi 2006), and to increased incidence of atypical melanocytic naevi (Bauer 2004; Csoma 2007).

Continuous phototherapy involves maintaining the jaundiced neonate under phototherapy virtually all the time with only minimal interruptions (e.g. during feeding or cleaning) so as to maximise the time spent under radiant energy and hopefully minimise the duration of phototherapy and hospital stay. Intermittent phototherapy involves regular cessation of phototherapy at specific times and for specific duration to reduce exposure to radiant energy and allow ample time for parental-infant interaction. There is no optimal time schedule for intermittent phototherapy defined in the literature and, therefore, different studies have looked at various time intervals for their effectiveness at lowering serum bilirubin.

## How the intervention might work

Photodegradation of bilirubin is a two-step phenomenon, where the first step is the rapid photochemical reaction at the skin level, followed by the slow migration of unbound bilirubin from the blood into the skin for ongoing photodegradation over a period of one to three hours (Brown 1980). Interruptions in phototherapy during this period, potentially causes few alterations in bilirubin levels and also allows for migration of bilirubin to proceed effectively. Hence, intermittent phototherapy, which involves regular cessation of phototherapy at specific times and for specific duration, appears to be a scientifically plausible alternative to continuous phototherapy. Also less phototherapy exposure with intermittent phototherapy could potentially result in fewer side effects, allay parental anxiety and improve nursing experience.

## Why it is important to do this review

There is no consensus on whether intermittent phototherapy or continuous phototherapy is the preferred method of treatment. Intermittent therapy has practical advantages including facilitating feeding and bonding, however, its effectiveness compared with continuous phototherapy is unknown. Therefore, the aim of this Cochrane Review is to systematically assess the available evidence from randomised and quasi-randomised controlled trials for the effectiveness of intermittent phototherapy compared to continuous phototherapy.

# OBJECTIVES

To assess the safety and effectiveness of intermittent phototherapy compared with continuous phototherapy

# METHODS

## Criteria for considering studies for this review

### Types of studies

We included randomised controlled trials (RCTs), cluster-RCTs and quasi-RCTs.

### Types of participants

We included infants (both term and preterm) up to the age of 30 days with jaundice or hyperbilirubinaemia requiring phototherapy.

### Types of interventions

We included intermittent phototherapy compared with continuous phototherapy by any method and at any dose and duration as defined by the authors.

### Types of outcome measures

#### *Primary outcomes*

- Rate of decline of serum bilirubin (micromol/L/h)

- Bilirubin-induced brain dysfunction (defined as either the pathological finding of deep-yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei or acute or chronic neurological deficit including athetoid cerebral palsy, impaired upward gaze and deafness or isolated conditions, such as auditory neuropathy or dyssynchrony)

***Secondary outcomes***

- Treatment failure i.e. the need to restart phototherapy or exchange transfusion or both
- Infant mortality - all cause
- Need for exchange transfusion
- Infant growth parameters e.g. weight gain (g/kg/day) and/or length (cm/day)
- Length of hospital stay (days) during treatment for hyperbilirubinaemia
- Infant feeding volumes (defined as volume of feeds per day while receiving phototherapy)
- Total duration of phototherapy - total number of hours of phototherapy delivered
- Duration of first episode of phototherapy (hours)
- Parental satisfaction with care - qualitative assessment of parental perception of effect of phototherapy
- Medical staff satisfaction with care - qualitative assessment of the perception of the medical staff on the effect of phototherapy

**Side effects**

- Dehydration (as defined by the authors)
- Gastrointestinal motility (defined as number of stools passed per day)
- Patent ductus arteriosus
- Thrombocytopenia (defined as platelet count < 100,000/µL)
- Retinal damage
- Melanocytic naevi
- Temperature instability - hypothermia/hyperthermia
- Rash
- Drowsiness
- Bronze discolouration of the skin
- Interference with maternal-infant interaction

## Search methods for identification of studies

### Electronic searches

Information Specialist, wrote search strategies for this review.

The following databases were searched without language, publication year, publication type, or publication status restrictions. Searches were conducted in January 2022 in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL 2022, Issue 1) in the Cochrane Library;
- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) (1946 to January 28, 2022);
- Ovid Embase (1974-January 28, 2022)

Search strategies are provided in Appendix 1; Appendix 2; Appendix 3.

We searched the following clinical trial registries for ongoing or recently completed trials:

- The World Health Organization's International Clinical Trials Registry Platform (ICTRP) (who.int/ictrp/search/en/);
- The U.S. National Library of Medicine's ClinicalTrials.gov (clinicaltrials.gov);
- The ISRCTN Registry (http://www.isrctn.com/).

This search updates methods included in the protocol (Onyango 2009; see Appendix 4 and Differences between protocol and review).

### Searching other resources

We also searched the reference lists of any articles selected for inclusion in this review in order to identify additional relevant articles.

## Data collection and analysis

We collected information regarding the method of randomisation, blinding, intervention, stratification and whether the trial was single or multicentre for each included study. We noted information regarding trial participants including gestational age at birth and postnatal age. We analysed the clinical outcomes noted above in Types of outcome measures.

### Selection of studies

We included all randomised, cluster-randomised and quasi-randomised controlled trials fulfilling our inclusion criteria. Two authors (SBG, TS) reviewed the results of the search and separately selected studies for inclusion. We resolved any disagreements by discussion and involvement of a third author when required (LL).

We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) (Moher 2009).

**Figure 1. PRISMA flow diagram**

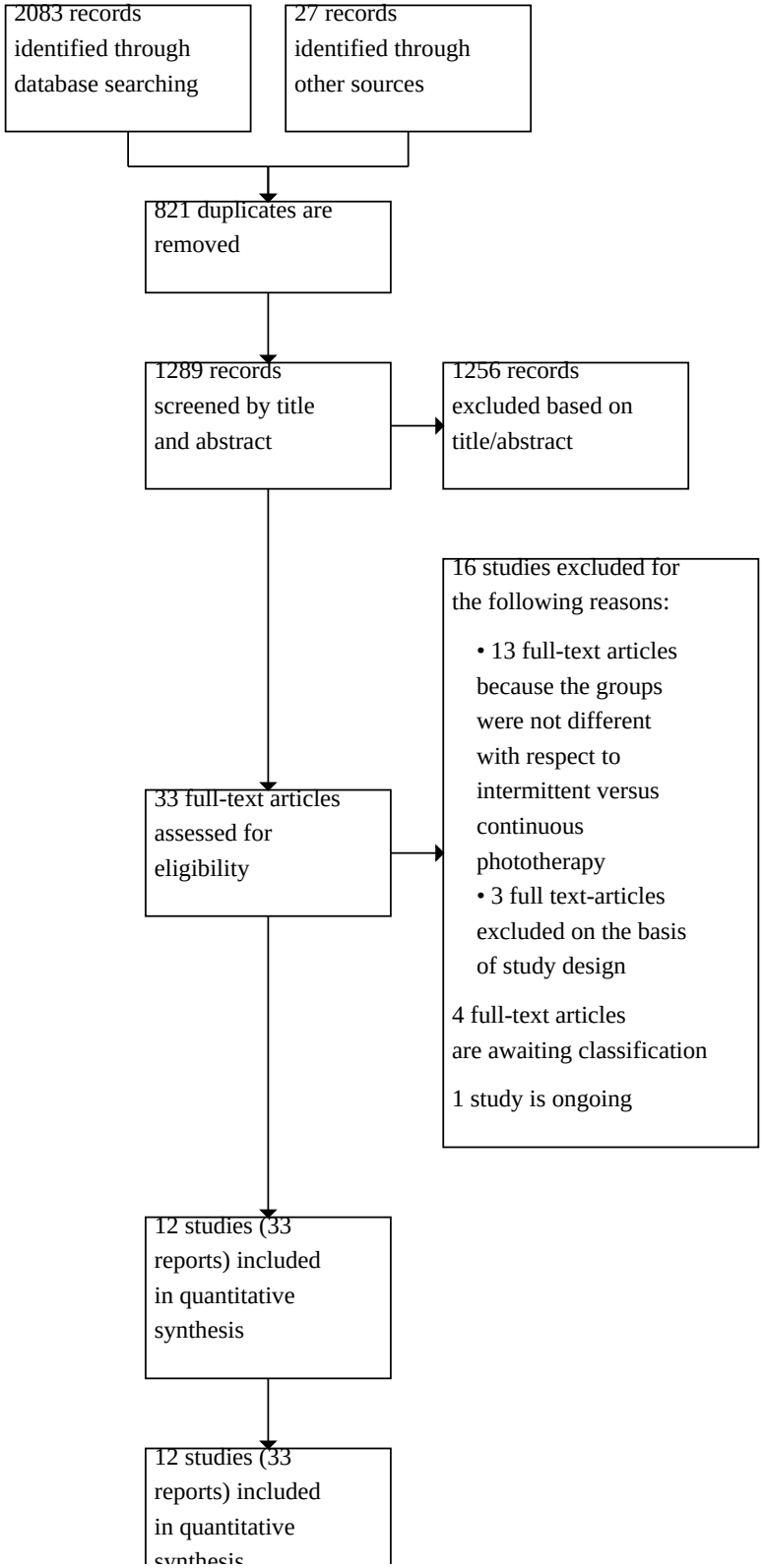


**Figure 1. (Continued)**

in quantitative synthesis (meta-analysis)

### Data extraction and management

Three review authors (SBG, TS, LL) extracted, assessed, and coded all data for each study, using a form designed specifically for this review. Two authors were assigned to each study. One review author (SBG) authored an included study (Gottimukkala 2021) and was not involved with data extraction and management for this study. We resolved any disagreements by involvement of a third author. We replaced any standard error of the mean by the corresponding standard deviation. Medians and interquartile ranges were converted to means and standard deviations. Standard deviations were imputed using average standard deviations from other studies when these were not reported. Two review authors (SBG, TS) entered final data for each study into Review Manager 5 (Review Manager 2020), which another review author (TS, LL) checked. All review authors reviewed the protocol, analysis and draft manuscript.

### Assessment of risk of bias in included studies

Two review authors (SBG, TS) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane Risk of bias tool (Higgins 2020).

The risk of bias was assessed based on the following:

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- any other bias.

We resolved any disagreements by discussion or by consulting a third author (LL). See Appendix 5 for a more detailed description of risk of bias for each domain.

### Measures of treatment effect

We used RevMan 5 for all data analyses. If it was possible to conduct a meta-analysis of identified trials, the effect measures for binary outcomes were the absolute risk difference (RD), with 95% confidence interval (CI). For the primary binary outcomes, number needed to treat for an additional beneficial outcome (NNTB) , or number needed to treat for an additional harmful outcome (NNTH), was calculated. For continuous outcomes, the effect measures was the mean difference (MD) or, if the scale of measurement differed across trials, the standardised mean difference (SMD), each with 95% CI.

### Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials and infants were considered only once in the analysis.

### Dealing with missing data

We carried out analysis on an intention-to-treat basis for all outcomes. We analysed all participants in the treatment group to which they were randomised, regardless of the actual treatment received. If we identified important missing data (in the outcomes) or unclear data, we requested the missing data by contacting the original investigators. We addressed the potential impact of missing data on the findings of the review in the Discussion section.

### Assessment of heterogeneity

If it was possible to conduct a meta-analysis, we estimated the amount of heterogeneity of treatment effect across trials using the $I^2$ statistic and the $Chi^2$ statistic.

### Assessment of reporting biases

We conducted a comprehensive search for eligible studies and we remained alert for duplication of data. We did not assess possible publication bias by inspection of a funnel plot, as we did not identify 10 or more trials for meta-analysis.

### Data synthesis

When we identified multiple studies that we considered to be sufficiently similar, we performed a meta-analysis using Review Manager 5 (Review Manager 2020). For categorical outcomes, we calculated the typical estimates RD, with its 95% CI; for continuous outcomes, we calculated the MD, with its 95% CI. We used a fixed-effect model to combine data where it was reasonable to assume that studies were estimating the same underlying treatment effect. If there was substantial heterogeneity ($I^2$ > 50%), we tried to explain this based on the different study characteristics and subgroup analyses.

### Subgroup analysis and investigation of heterogeneity

We considered the following groups for subgroup analysis where data were available:

- gestational age: term (≥ 37 weeks) versus preterm (< 37 weeks);
- aetiology of jaundice: haemolytic versus non-haemolytic;
- radiant energy, as defined by the authors;
- various regimens of intermittent phototherapy (intermittent phototherapy regimens where phototherapy is used for < two hours at a time versus regimens where phototherapy is used for ≥ two hours at a time);
- trial validity (industry-funded versus non-industry-funded trials)

We restricted these analyses to the primary outcomes.

If substantial heterogeneity ($I^2 > 50\%$) was present, we explored its sources, considering differences in design or clinical features of the trials. We interpreted the results of the meta-analyses accordingly; and we downgraded the certainty of evidence in the Summary of findings 1, according to the GRADE recommendations.

### Sensitivity analysis

Where we identified substantial heterogeneity, we conducted sensitivity analysis to determine if the findings were affected by inclusion of only those trials considered to have used adequate methodology with a low risk of bias (for selection and performance bias). We reported the results of sensitivity analyses for primary outcomes only.

### Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence for the following (clinically relevant) outcomes:

- Bilirubin-induced brain dysfunction (defined as either the pathological finding of deep-yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei or acute or chronic neurological deficit including athetoid cerebral palsy, impaired upward gaze and deafness or isolated conditions, such as auditory neuropathy or dyssynchrony);
- rate of decline of serum bilirubin (micromol/L/h);
- treatment failure i.e. the need to restart phototherapy or exchange transfusion or both;
- infant mortality - all cause.

Two review authors (SBG, TS) independently assessed the certainty of the evidence for each of the outcomes above. We considered evidence from RCTs as high certainty, downgrading the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates (power calculations used to determine optimal information size) and presence of publication bias. We used GRADEpro GDT to create Summary of findings 1 and report the certainty of the evidence.

The GRADE approach results in an assessment of the certainty of a body of evidence as one of four grades.

- High certainty: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low certainty: we are very uncertain about the estimate.

## RESULTS

### Description of studies

See PRISMA diagram in Figure 1.

### Results of the search

Searches identified 2110 references (2083 from databases; 25 from trial registries; 2 from reference checking). After removing 821 duplicates, 1289 records were available for screening. We excluded 1256 records during title abstract screening and reviewed 33 full texts.

We included 12 studies: Arnold 2020; Caldera 1984; Gottimukkala 2021; Khalid 2017; Lau 1984; Maurer 1973; Niknafs 2008;Patil 2020; Romagnoli 1976; Sachdeva 2015; Taheritafti 2019; Wu 1974), and excluded 16 excluded (Broughton 1965; Bryla 1985; Elliot 1974; Goudarzvand 2019; Hodgman 1970; Komar-Szymborska 1994; Krueger Jr 2001; Ludington-Hoe 2001; Martinez 1992; Morris 2008; Namnabati 2019; Tabb 1972; Vogl 1978; Woodall 1992; Yilmaz 2015; Zainab 2004).

We assessed four studies as awaiting classification (CTRI/2012/09/002968; IRCT201012255459N1; Khaliq 2016; Suri 2019). Two studies reported identical results (Khaliq 2016; Suri 2019), and we are awaiting a response from the respective authors and editors (see Characteristics of studies awaiting classification).

We assessed one study as ongoing (NCT03927833). This study is enrolling preterm infants with non-haemolytic jaundice and randomising to either intermittent or continuous phototherapy (see Characteristics of ongoing studies).

### Included studies

We assessed 12 studies including a total of 1600 infants that randomised newborn infants to either intermittent or continuous phototherapy (see Characteristics of included studies).

#### *Types of participants*

##### Gestational age at birth

- Eight studies enrolled term and near term infants (Caldera 1984; Gottimukkala 2021; Khalid 2017; Lau 1984; Niknafs 2008; Patil 2020; Sachdeva 2015; Taheritafti 2019).
- Four studies enrolled preterm infants (Arnold 2020; Maurer 1973; Romagnoli 1976; Wu 1974).

##### Aetiology of jaundice

- All studies enrolled infants with non-haemolytic jaundice.

#### *Types of interventions*

Continuous phototherapy consistently involved phototherapy continuously during the study period (with the exception of feeding). Studies followed different regimens for intermittent phototherapy group as follows:

- Four studies (Maurer 1973; Romagnoli 1976; Sachdeva 2015; Wu 1974): 12 hours on, 12 hours off;
- Arnold 2020 (two intermittent groups): 15 minutes or more per hour, adjusted daily based on total serum bilirubin levels; 30 minutes or more per hour, adjusted daily based on total serum bilirubin levels;
- Caldera 1984 (two intermittent groups): six hours on, six hours off; 30 minutes on, 30 minutes off;
- Gottimukkala 2021: one hour on, two hours off;
- Khalid 2017: one hour on, 30 minutes off;

- Lau 1984 (two intermittent groups): four hours on, four hours off; one hour on, three hours off;
- Niknafs 2008: one hour on, one hour off;
- Patil 2020: three hours on, three hours off;
- Taheritafti 2019: 18 hours on, eight hours off.

#### *Outcomes*

Ten of the 12 included studies reported rate of decline of serum bilirubin (Caldera 1984; Gottimukkala 2021; Khalid 2017; Maurer 1973; Niknafs 2008; Patil 2020; Romagnoli 1976; Sachdeva 2015; Taheritafti 2019; Wu 1974). One study specifically reported BIND as an outcome (Taheritafti 2019). One study (Sachdeva 2015) reported treatment failure. Seven studies reported mortality (Arnold 2020; Khalid 2017; Lau 1984; Niknafs 2008; Sachdeva 2015; Taheritafti 2019; Wu 1974). Two studies reported on need for exchange transfusion (Arnold 2020; Romagnoli 1976). Two studies reported weight gain (Romagnoli 1976; Wu 1974), however, data were only able to be included for one study (Romagnoli 1976). One study reported on differences in linear growth but did not provide data (Romagnoli 1976). Three studies reported length of hospital stay (Patil 2020; Sachdeva 2015; Taheritafti 2019). Two studies reported on feed volumes (Romagnoli 1976; Wu 1974). Eight studies reported on total duration of phototherapy (Arnold 2020; Caldera 1984; Gottimukkala 2021; Lau 1984; Niknafs 2008; Patil 2020; Sachdeva 2015; Taheritafti 2019), however, one study did not have sufficient detail for inclusion (Patil 2020). Six studies reported on duration of first episode of phototherapy (Caldera 1984; Gottimukkala 2021; Lau 1984; Niknafs 2008; Sachdeva 2015; Taheritafti 2019). One study reported on parental and staff satisfaction with care (Gottimukkala 2021). With respect to side effects, one study reported on patent ductus arteriosus (Arnold 2020) and one study reported on gastrointestinal dysmotility and rash (Gottimukkala 2021). No studies reported on dehydration, incidence of thrombocytopenia, retinal damage, melanocytic naevi, temperature instability, drowsiness, bronze discolouration of the skin, or interference with maternal-infant interaction.

### Excluded studies

We excluded 16 studies for the following reasons:

- We found three studies to be non-randomised on full-text review (Komar-Szymborska 1994; Vogl 1978; Zainab 2004);
- We found 13 studies where the groups were not different with respect to intermittent versus continuous phototherapy (Broughton 1965; Bryla 1985; Elliot 1974; Goudarzvand 2019; Hodgman 1970; Krueger Jr 2001; Ludington-Hoe 2001; Martinez 1992; Morris 2008; Namnabati 2019; Tabb 1972; Woodall 1992; Yilmaz 2015).

(See Characteristics of excluded studies).

## Risk of bias in included studies

Of the 12 studies that we included in the analysis, we considered four to have used adequate methodology with a low risk of selection and performance bias (Arnold 2020; Gottimukkala 2021; Khalid 2017; Sachdeva 2015). The other eight studies all had methodological concerns which we have documented below.

See Risk of bias graph (Figure 2), and Risk of bias summary (Figure 3).

**Figure 2.**

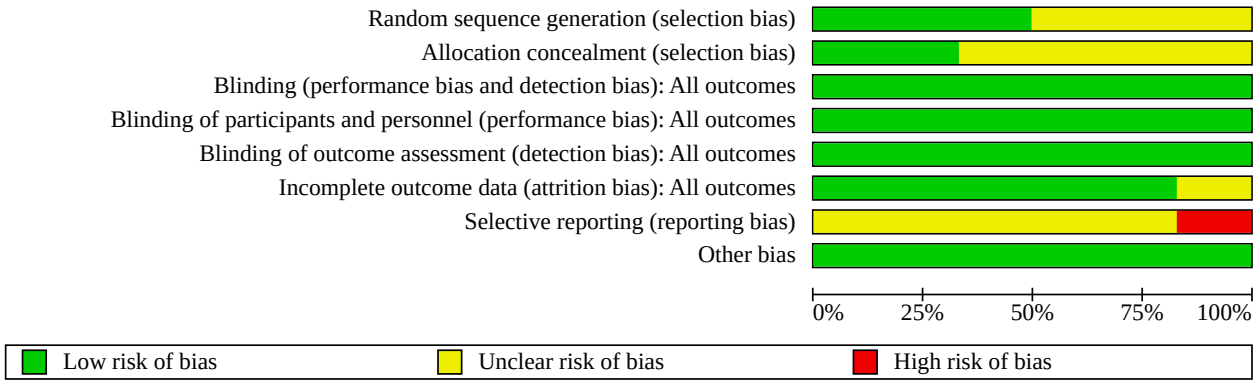
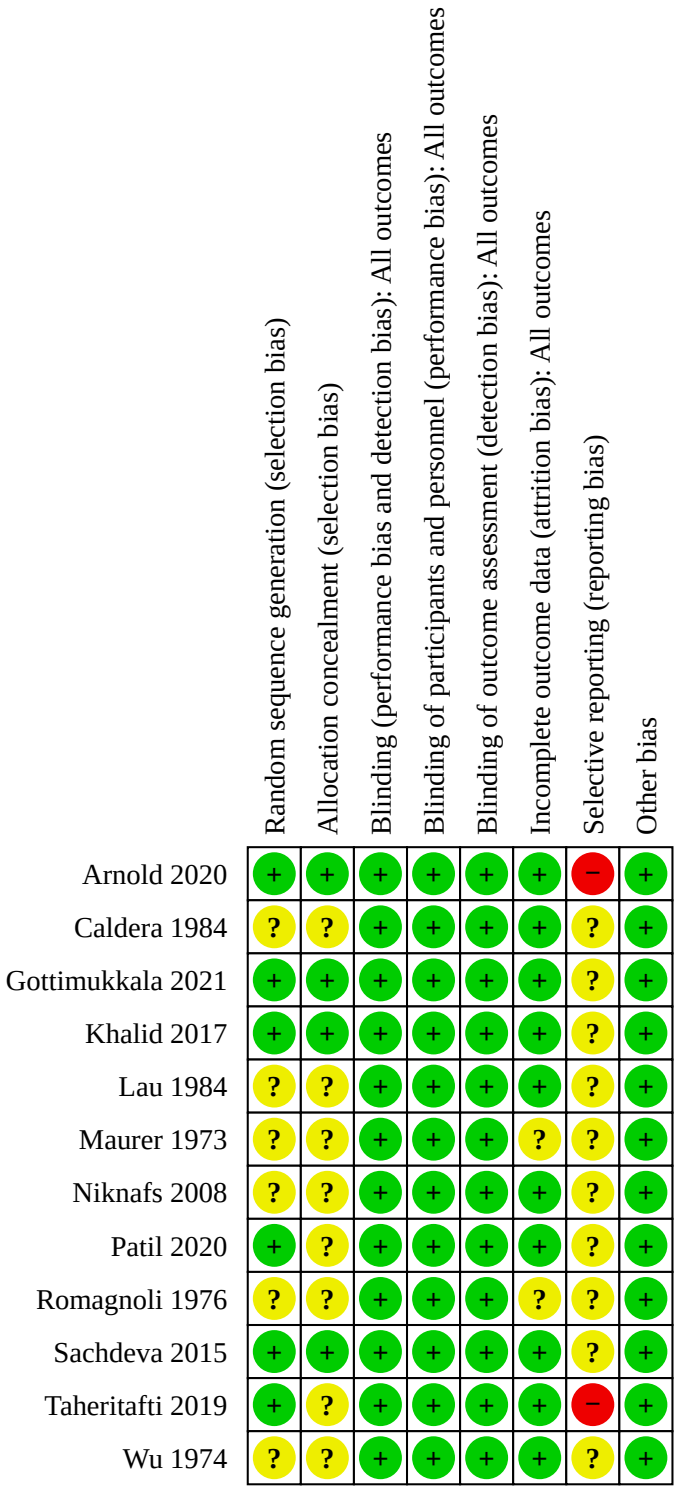


**Figure 3.**



### Allocation

We assessed random sequence generation to be unclear for six studies due to incomplete reporting (Caldera 1984; Lau 1984; Maurer 1973; Niknafs 2008; Romagnoli 1976; Wu 1974). It was at low risk for the other six studies (Arnold 2020; Gottimukkala 2021; Khalid 2017; Patil 2020; Sachdeva 2015; Taheritafti 2019). We assessed allocation concealment to be unclear for eight studies due to incomplete reporting (Caldera 1984; Lau 1984; Maurer 1973; Niknafs 2008; Patil 2020; Romagnoli 1976; Taheritafti 2019; Wu 1974). It was at low risk for the other four studies (Arnold 2020; Gottimukkala 2021; Khalid 2017; Sachdeva 2015).

### Blinding

We assessed all 12 included studies as being at low risk of performance and detection bias for most outcomes. All studies were unblinded but had objective primary outcome measures. Parental and medical staff satisfaction was reported in one study (Gottimukkala 2021) and this had an unclear risk of performance and detection bias.

### Incomplete outcome data

Ten of the 12 included studies reported complete outcome data for all infants (Arnold 2020; Caldera 1984; Gottimukkala 2021; Khalid 2017; Lau 1984; Niknafs 2008; Patil 2020; Sachdeva 2015; Taheritafti 2019; Wu 1974). We judged attrition bias to be unclear for two studies, due to incomplete reporting (Maurer 1973; Romagnoli 1976).

### Selective reporting

We assessed one study as being at high risk for reporting bias as it reported data at different time points to prespecified time points in the trial registry (Taheritafti 2019). We assessed one study (registered prospectively) as being at high risk for reporting bias. This was because the primary outcomes reported did not match the primary and secondary outcomes listed in the trial registry (Arnold 2020). All of the other studies were not registered prospectively, and we assessed them as having unclear risk of bias.

### Other potential sources of bias

No studies reported commercial sponsorship or affiliation.

A pre-planned subgroup analysis based on radiant energy was not possible as this was not consistently reported.

We identified no other potential sources of bias.

## Effects of interventions

See: **Summary of findings 1** Intermittent phototherapy compared to continuous phototherapy for neonatal jaundice

### Intermittent phototherapy versus continuous phototherapy (Comparison 1)

See Summary of findings 1.

#### *Primary outcomes*

##### Rate of decline of bilirubin (micromol/L/hr)

Meta-analysis of 10 studies found little or no difference in rate of decline of bilirubin (MD -0.09 micromol/L/hr, 95% CI -0.21 to 0.03; $I^2$ = 61%; 1225 infants; Analysis 1.1) (Caldera 1984; Gottimukkala 2021; Khalid 2017; Maurer 1973; Niknafs 2008; Patil 2020; Romagnoli 1976; Sachdeva 2015; Taheritafti 2019; Wu 1974). We rated this as low-certainty evidence due to moderate heterogeneity, and not meeting optimal information size.

##### Bilirubin-induced brain dysfunction (BIND)

One study reported no incidence of BIND (60 infants) (Taheritafti 2019; Analysis 1.2). It is uncertain whether either intermittent or continuous phototherapy reduces BIND because the certainty of this evidence is very low (no reported events from a single study).

#### *Secondary outcomes*

##### Treatment failure

One study reported no difference in treatment failure (RD 0.03, 95% CI -0.08 to 0.15; RR 1.63, 95% CI 0.29 to 9.17; 75 infants; heterogeneity not applicable; Analysis 1.3) (Sachdeva 2015). It is uncertain whether either intermittent or continuous phototherapy reduces treatment failure because the certainty of this evidence is very low (effect size that included both appreciable benefit and appreciable harm from a single study).

##### Infant mortality

Meta-analysis of 10 studies found little or no difference in infant mortality (RD -0.01, 95% CI -0.03 to 0.01; $I^2$ = 0%; RR 0.69, 95% CI 0.37 to 1.31; 1470 infants; Analysis 1.4) (Arnold 2020; Caldera 1984; Gottimukkala 2021; Khalid 2017; Lau 1984; Niknafs 2008; Patil 2020; Sachdeva 2015; Taheritafti 2019; Wu 1974). We rated this as low-certainty evidence due to not meeting optimal information size with an effect size that included both appreciable benefit and appreciable harm.

##### Need for exchange transfusion

Meta-analysis of two studies found no incidence of exchange transfusion (RD 0.00, 95% CI -0.02 to 0.02; RR not estimable; $I^2$ = 0%; 364 infants; Analysis 1.5) (Arnold 2020; Romagnoli 1976).

##### Weight gain (g/kg/day)

One study reported no difference in weight gain (MD -3.71 g/kg/day, 95% CI -10.25 to 2.82; 59 infants; heterogeneity not applicable; Analysis 1.6) (Romagnoli 1976). One additional study reported weight gain, but there were insufficient data reported to allow conversion of data (Wu 1974).

##### Linear growth

One study reported no difference in linear growth, but did not provide data (Romagnoli 1976).

##### Length of hospital stay (days)

Meta-analysis of three studies found no difference in length of hospital stay (MD -0.07 days, 95% CI -0.22 to 0.09; $I^2$ = 0%; 325 infants; Analysis 1.7) (Patil 2020; Sachdeva 2015; Taheritafti 2019).

##### Infant feeding volumes (volume of feeds per day while receiving phototherapy)

Meta-analysis of two studies found no difference in infant feeding volumes (MD -0.82 mL, 95% CI -8.80 to 7.16; $I^2$ = 0%; 136 infants; Analysis 1.8) (Romagnoli 1976; Wu 1974).

#### Total irradiation time (hours)

Meta-analysis of seven studies found a significant decrease in the total number of hours under phototherapy with intermittent phototherapy (MD -15.27 hours, 95% CI -16.42 to -14.12; $I^2$ = 91%; 917 infants; Analysis 1.9) (Arnold 2020; Caldera 1984; Gottimukkala 2021; Lau 1984; Niknafs 2008; Sachdeva 2015; Taheritafti 2019).

#### Duration of first episode of phototherapy (hours)

Meta-analysis of six studies found no difference in the total duration of the first episode of phototherapy (including periods off in the intermittent groups) (MD -0.89 hours, 95% CI -2.50 to 0.72; $I^2$ = 65%; 629 infants; Analysis 1.10) (Caldera 1984; Gottimukkala 2021; Lau 1984; Niknafs 2008; Sachdeva 2015; Taheritafti 2019).

#### Parental satisfaction with care (score out of 10)

One study reported improved parental satisfaction with care with intermittent phototherapy (MD 2.00 [score out of 10], 95% CI 1.56 to 2.44; heterogeneity not applicable; 174 infants; Analysis 1.11), (Gottimukkala 2021).

#### Medical staff satisfaction with care (score out of 10)

One study reported improved medical staff satisfaction with care with continuous phototherapy (MD -2.00 [score out of 10], 95% CI -2.35 to -1.65; heterogeneity not applicable; 174 infants; Analysis 1.12) (Gottimukkala 2021).

### *Side effects*

#### Gastrointestinal dysmotility

One study reported no difference in the incidence of gastrointestinal dysmotility (RD -0.01, 95% CI -0.06 to 0.04; RR 0.70, 95% CI 0.12 to 4.07; heterogeneity not applicable; 174 infants; Analysis 1.13) (Gottimukkala 2021).

#### Patent ductus arteriosus

One study reported no difference in the incidence of patent ductus arteriosus (RD -0.02, 95% CI -0.12 to 0.08; RR 0.92, 95% CI 0.60 to 1.41; heterogeneity not applicable; 271 infants; Analysis 1.14) (Arnold 2020).

#### Rash

One study reported no difference in the incidence of rash (RD -0.01, 95% CI -0.07 to 0.05; RR 0.79, 95% CI 0.18 to 3.41; heterogeneity not applicable; 174 infants; Analysis 1.15) (Gottimukkala 2021).

No studies reported on dehydration, thrombocytopenia, retinal damage, melanocytic naevi, temperature instability, drowsiness, bronze discolouration of the skin, or interference with maternal-infant interaction.

### *Subgroup analysis: intermittent phototherapy versus continuous phototherapy: term infants versus preterm infants*

#### Term infants

#### Rate of decline of bilirubin (micromol/L/hr)

Meta-analysis of seven studies found no difference in the rate of decline of bilirubin (MD -0.04 micromol/L/hr, 95% CI -0.17 to 0.0.09; $I^2$ = 65%; 1049 infants; Analysis 2.1) (Caldera 1984; Gottimukkala 2021; Khalid 2017; Niknafs 2008; Patil 2020; Sachdeva 2015; Taheritafti 2019).

#### BIND

One study reported no incidence of BIND (60 infants; Analysis 2.2) (Taheritafti 2019).

#### Preterm infants

#### Rate of decline of bilirubin (micromol/L/hr)

Meta-analysis of three studies found an increase in the rate of decline of bilirubin with continuous phototherapy (MD -0.51 micromol/L/hr, 95% CI -0.86 to -0.15; $I^2$ = 0%; 176 infants; Analysis 2.1) (Maurer 1973; Romagnoli 1976; Wu 1974).

#### BIND

No studies reported on the incidence of BIND.

### *Subgroup analysis: intermittent phototherapy versus continuous phototherapy: intermittent phototherapy regimen (phototherapy on for < two hours versus ≥ two hours)*

#### Phototherapy on for < two hours

#### Rate of decline of bilirubin (micromol/L/hr)

Meta-analysis of four studies found no difference in the rate of decline of bilirubin (MD -0.06 micromol/L/hr, 95% CI -0.20 to 0.09; $I^2$ = 56%; 713 infants; Analysis 3.1) (Caldera 1984; Gottimukkala 2021; Khalid 2017; Niknafs 2008).

#### BIND

No studies reported on the incidence of BIND.

#### Phototherapy on for ≥ two hours

#### Rate of decline of bilirubin (micromol/L/hr)

Meta-analysis of seven studies found no difference in the rate of decline of bilirubin (MD -0.17 micromol/L/hr, 95% CI -0.36 to 0.02, $I^2$ = 61%; 581 infants; Analysis 3.1) (Caldera 1984; Maurer 1973; Patil 2020; Romagnoli 1976; Sachdeva 2015; Taheritafti 2019; Wu 1974).

#### BIND

One study reported no incidence of BIND (60 infants) (Taheritafti 2019).

#### Sensitivity analysis

#### Rate of decline of bilirubin (micromol/L/hr)

Meta-analysis of three studies found no difference in the rate of decline of bilirubin (MD 0.02 micromol/L/hr, 95% CI -0.14 to 0.19, $I^2$ = 82%; 549 infants; Analysis 4.1) (Gottimukkala 2021; Khalid 2017; Sachdeva 2015).

#### BIND

No studies included in the sensitivity analysis reported on the incidence of BIND.

## DISCUSSION

See Summary of findings table 1

### Summary of main results

#### Primary outcomes

Evidence from 10 RCTs, involving 1225 infants, showed little or no difference between intermittent phototherapy and continuous

phototherapy with respect to reducing bilirubin levels in jaundiced newborn infants (low-certainty evidence) (Caldera 1984; Gottimukkala 2021; Khalid 2017; Maurer 1973; Niknafs 2008; Patil 2020; Romagnoli 1976; Sachdeva 2015; Taheritafti 2019; Wu 1974). In subgroup analysis, preterm infants (3 studies, involving 176 infants) had an increase in rate of bilirubin decline with continuous phototherapy (MD -0.51 micromol/L/hr, 95% CI -0.86 to -0.15; $I^2$ = 0%) (Maurer 1973; Romagnoli 1976; Wu 1974). Term infants (7 studies, involving 1049 infants) showed no difference in the rate of bilirubin decline (MD -0.04 micromol/L/hr, 95% CI -0.17 to 0.09; $I^2$ = 65%) (Caldera 1984; Gottimukkala 2021; Khalid 2017; Niknafs 2008; Patil 2020; Sachdeva 2015; Taheritafti 2019). Different intermittent phototherapy regimens (phototherapy on < two hours versus ≥ two hours) showed no difference in the rate of bilirubin decline. With respect to bilirubin-induced brain dysfunction, only one study involving 60 infants reported no incidence of this outcome (very low-certainty evidence) (Taheritafti 2019).

### Secondary outcomes

Evidence from 10 RCTs involving 1470 infants showed little or no difference between intermittent phototherapy and continuous phototherapy with respect to mortality (low-certainty evidence) (Arnold 2020; Caldera 1984; Gottimukkala 2021; Khalid 2017; Lau 1984; Niknafs 2008; Patil 2020; Sachdeva 2015; Taheritafti 2019; Wu 1974). Only one study involving 75 infants reported no difference in treatment failure (very low-certainty evidence) (Sachdeva 2015), and only two studies involving 364 infants reported on the need for exchange transfusion (Arnold 2020; Romagnoli 1976). There were no differences observed in growth or feeding volumes during phototherapy. There was a significant decrease in the total duration of phototherapy with intermittent phototherapy (7 studies; 917 infants; MD -15.27 hours, 95% CI -16.42 to -14.12; $I^2$ = 91%) (Arnold 2020; Caldera 1984; Gottimukkala 2021; Lau 1984; Niknafs 2008; Sachdeva 2015; Taheritafti 2019), however, there was no difference in the duration of the first episode of phototherapy (including periods off in the intermittent groups) (6 studies; 629 infants; MD -0.89 hours, 95% CI -2.50 to 0.72; $I^2$ = 65%), (Caldera 1984; Gottimukkala 2021; Lau 1984; Niknafs 2008; Sachdeva 2015; Taheritafti 2019). There was no difference in the length of hospital stay (3 studies, involving 325 infants) (Caldera 1984; Sachdeva 2015; Taheritafti 2019). One study involving 174 infants reported parental satisfaction was higher with intermittent phototherapy whereas staff satisfaction was higher with continuous phototherapy (Gottimukkala 2021). Most prespecified side effects were not reported. One study involving 174 infants reported on the incidence of gastrointestinal dysmotility and rash (Gottimukkala 2021). One study involving 271 infants reported on the incidence of patent ductus arteriosus (Arnold 2020).

## Overall completeness and applicability of evidence

There are significant limitations in the overall completeness and applicability of the evidence. There were 12 RCTs eligible for inclusion in the review, involving a total of 1600 infants. It is unlikely that the optimal information size has been reached for any outcome. The differing population groups studied and markedly different phototherapy regimens resulted in significant heterogeneity between the studies. Specifically, there are marked differences between older studies that investigated the effects of early phototherapy in preterm infants over the first days of life and more recent studies that investigate the effects of phototherapy in term infants that have reached higher bilirubin thresholds. Subgroup analyses only partially address these issues as the information size is further diminished. Although it is reassuring that there were no significant differences observed in the rate of decline in bilirubin, there are important safety outcomes that were inadequately covered in the available evidence.

Most studies reported on the primary outcome of rate of decline of bilirubin, however, this outcome has less relevance in preterm populations which are often treated at lower thresholds at an early postnatal age (when bilirubin levels are expected to be rising). We found that studies involving preterm infants commonly report peak bilirubin, which may be more relevant in this subgroup.

## Quality of the evidence

Four studies were assessed as having adequate methodology with a low risk of selection and performance bias and were included in a sensitivity analysis (Arnold 2020; Gottimukkala 2021; Khalid 2017; Sachdeva 2015). Of the 12 studies included in the review, eight were at unclear risk of allocation bias (Caldera 1984; Lau 1984; Maurer 1973; Niknafs 2008; Patil 2020; Romagnoli 1976; Taheritafti 2019; Wu 1974). All studies were considered at low risk of performance and detection bias as all reported outcome measures that were objective. There were no significant concerns regarding attrition bias. All studies were assessed as having either unclear or high risk of reporting bias. Only one study was registered prospectively (Arnold 2020), which raises a substantial risk of publication bias.

It is unclear if the decrease in number of hours of phototherapy is clinically important. Similarly, it is unclear whether any effect on the rate of bilirubin decline in preterm infants is clinically meaningful. The risks of continuous phototherapy and the potential benefits of a slightly lower bilirubin level are unknown. Although there are theoretical benefits to intermittent regimens, there were no objective advantages identified in this review.

We graded the certainty of the evidence for rate of decline of bilirubin as low with downgrading due to moderate heterogeneity and not meeting optimal information size. We graded the certainty of the evidence for bilirubin-induced brain dysfunction as very low as there were no reported events from a single study. We graded the certainty of the evidence for treatment failure as very low as the effect size included both appreciable benefit and appreciable harm from a single study. We graded the certainty of the evidence for mortality as low with downgrading due to not meeting optimal information size with an effect size that included both appreciable benefit and appreciable harm (see Summary of findings 1).

## Potential biases in the review process

We conducted extensive searches of the published and unpublished literature for trials comparing intermittent phototherapy with continuous phototherapy in jaundiced infants. Three review authors (SBG, TS, LL) independently assessed the trials and extracted data. We prespecified all primary and secondary outcomes reported and all subgroup analyses. The authors of this review have no financial or material conflicts of interest to report.

### Agreements and disagreements with other studies or reviews

We found no related Cochrane meta-analysis reporting on intermittent phototherapy compared with continuous phototherapy in jaundiced infants. One systematic review and meta-analysis reported on intermittent versus continuous phototherapy (Chu 2021). The review analysed four studies, two of which have been included in this review (Lau 1984 [based on results provided in the review as not referenced]; Sachdeva 2015). The remaining two studies were a retrospective cohort study (Zhou 2019) and a study appearing to compare two different intermittent regimens (unable to locate as not referenced correctly). The review found no difference in treatment efficacy but a decrease in phototherapy duration and side effects (not specified) with intermittent phototherapy. The National Institute for Health and Care Excellence (NICE) (2020) guideline for jaundice in newborn infants suggested that there was no clear evidence of differences between intermittent and continuous phototherapy (NICE 2020). This was based on the findings of one study, which is included in this review (Lau 1984).

## AUTHORS' CONCLUSIONS

### Implications for practice

The available evidence detected no difference between intermittent and continuous phototherapy with respect to rate of decline of bilirubin. Intermittent phototherapy is associated with a decrease in the total number of hours of phototherapy exposure. There are theoretical benefits to intermittent regimens but there are important safety outcomes that were inadequately addressed. Although there is insufficient safety data to guide universal practice, the evidence suggests that it would be reasonable in cases of mild physiological jaundice to have short breaks from phototherapy to facilitate parental bonding, breastfeeding and rest.

### Implications for research

Large, well-designed, prospective trials are needed before it can be concluded that intermittent and continuous phototherapy regimens are equally effective. High-quality trials are needed in both preterm and term infants. Future trials should focus on reporting objective, measurable clinical outcomes and safety data.

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As a Cochrane Neonatal Associate Editor, Bill McGuire has peer reviewed and offered feedback for this review.

The methods section of the review is based on a standard template used by Cochrane Neonatal.

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* Indicates the major publication for the study

# CHARACTERISTICS OF STUDIES

## Characteristics of included studies *[ordered by study ID]*

### Arnold 2020

| ***Study characteristics*** | |
|---|---|
| Methods | Multicentre, randomised controlled trial conducted in USA |
| Participants | **Inclusion criteria:** birth weight 401 to 1000 grams; postnatal age < 24 hours; receiving full medical support<br><br>**Exclusion criteria:** previously received phototherapy; known haemolytic disease; overt nonbacterial infection; major anomaly; moribund (pH < 6.8 for > 2 hours or persistent bradycardia < 100 beats per minute associated with hypoxia for > 2 hours) |
| Interventions | Total N = 305<br><br>**Group 1 (n = 137):** intermittent phototherapy (15 minutes or more per hour, adjusted based on daily total serum bilirubin levels)<br><br>**Group 2 (n = 34):** intermittent phototherapy (30 minutes or more per hour, adjusted based on daily total serum bilirubin levels)<br><br>**Group 3 (n = 134):** continuous phototherapy |

**Arnold 2020** *(Continued)*

| | |
|---|---|
| | Infants in all groups received phototherapy when the total serum bilirubin was ≥ 5.0 mg/dL during the first 14 days of life (infants 751 to 1000 grams ≥ 7.0 mg/dL days 8 to 14) |
| Outcomes | **Primary outcomes**<br>• Mean peak total serum bilirubin levels<br>• Mean phototherapy hours<br>**Reported outcomes**<br>• Death and major predischarge morbidities, including:<br>  ○ severe (grade 3 or 4) intraventricular haemorrhage;<br>  ○ bronchopulmonary dysplasia;<br>  ○ surgical necrotising enterocolitis;<br>  ○ patent ductus arteriosus requiring treatment;<br>  ○ severe retinopathy of prematurity (stage 3 or higher or plus disease);<br>  ○ late onset sepsis. |
| Notes | clinicaltrials.gov identifier: **NCT01944696** |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Participants were ... randomized using a variable block size and a web-based computerized program (REDCap)". |
| Allocation concealment (selection bias) | Low risk | Quote: "Participants were ... randomized using a variable block size and a web-based computerized program (REDCap)". |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "The BAERs were assessed by a single evaluator (A.D.) using carefully standardized methods and blinded to treatment group". |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete outcome data provided for all infants |
| Selective reporting (reporting bias) | High risk | Primary outcomes reported did not match primary and secondary outcomes in trial registry.<br>NCT01944696: Cycled phototherapy: a safer effective treatment for small premature infants? clinicaltrials.gov/ct2/show/NCT01944696 (first received 18 September 2013). |
| Other bias | Low risk | No other potential sources of bias were identified. |

### Caldera 1984

| ***Study characteristics*** | |
|---|---|
| Methods | Single-centre, randomised controlled trial conducted in France |
| Participants | **Inclusion criteria:** (quote:) "children hospitalised for intense jaundice during the first ten days of life"<br><br>**Exclusion criteria:** (quote) "septicaemic infections, severe respiratory distress, jaundice due to haemolytic and metabolic anaemia" |
| Interventions | Total N = 172<br><br>**Group 1 (n = 69):** continuous phototherapy<br><br>**Group 2 (n = 47):** intermittent phototherapy (6 hours on, 6 hours off)<br><br>**Group 3 (n = 56):** intermittent phototherapy (0.5 hours on, 0.5 hours off)<br><br>Infants received phototherapy when total bilirubin > 200 umol/L and continued until total bilirubin < 200 umol/L |
| Outcomes | Primary outcome<br><br>• Not specified<br><br>Reported outcomes<br><br>• Duration of phototherapy<br>• Average daily decrease in bilirubin<br>• Percentage daily decrease in bilirubin |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation not described (Quote: "The distribution according to the treatment mode ... was carried out at random"). |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment not described |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete outcome data provided for all infants |

**Caldera 1984** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| Other bias | Low risk | No other potential sources of bias were identified. |

**Gottimukkala 2021**

| ***Study characteristics*** | |
|---|---|
| Methods | Single-centre, randomised controlled trial conducted in India |
| Participants | **Inclusion criteria:** term infants (gestational age ≥ 35 weeks); birth weight ≥ 2000 grams; (quote:) "serum bilirubin ... at a level requiring PT, as decided by the treating clinician"<br><br>**Exclusion criteria:** (quote:) "needing immediate exchange transfusion"; (quote:) "significant haemolytic jaundice"; major congenital anomalies; birth asphyxia; significant haemodynamic instability; significant conjugated hyperbilirubinaemia; infants who had already received > 5 hours of phototherapy |
| Interventions | Total N = 174<br><br>**Group 1 (n = 89):** continuous phototherapy<br><br>**Group 2 (n = 85):** intermittent phototherapy (1 hour on, 2 hours off)<br><br>Phototherapy was initiated at (quote:) "2 mg/dL less than the threshold suggested by American Academy of Pediatrics (AAP) guidelines"<br><br>Phototherapy was discontinued if bilirubin levels were < 6 mg/dL on day 1; < 10 mg/dL on day 2; < 13 mg/dL after day 2 |
| Outcomes | **Primary outcome**<br><br>• Rate of fall of bilirubin<br><br>**Secondary outcomes**<br><br>• Duration of phototherapy<br>• Maternal satisfaction score<br>• Nusing satisfaction score<br>• Clinical side effects ((quote:) "hypo/hyperthermia, rash, hypotension, increased stooling", biochemical abnormalities) |
| Notes | CTRI registration number: CTRI/2018/01/011072 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "enrolled infants ... were then randomly allocated to receive either IPT or CPT. The random sequence was generated online from the website *http://www.randomization.com* (accessed on 12/07/2016) ..." |
| Allocation concealment (selection bias) | Low risk | Quote: "The random sequence was generated ... by the Allied Health Science Department Head and serially numbered opaque sealed envelopes in block sizes of 8 were prepared. The primary investigator then allocated the groups by opening the identical envelopes containing the treatment code". |

**Gottimukkala 2021** *(Continued)*

| | | |
|---|---|---|
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete outcome data provided for all infants |
| Selective reporting (reporting bias) | Unclear risk | Trial registered retrospectively |
| Other bias | Low risk | No other potential sources of bias were identified. |

**Khalid 2017**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Single-centre, randomised controlled trial conducted in Pakistan |
| Participants | **Inclusion criteria:** (quote:) "Full term"; postnatal age 24 hours to 10 days; unconjugated bilirubin 12 to 20, Apgar score > 6 at 5 minutes<br>**Exclusion criteria:** (quote:) "Ventilator support"; peritoneal dialysis; congenital abnormality |
| Interventions | Total N = 300 patients<br>**Group A (n = 150):** continuous phototherapy (2 hours on, 20 minutes off)<br>**Group B (n = 150):** intermittent phototherapy (1 hour on, 30 minutes off)<br>Phototherapy was continued for 36 hours. |
| Outcomes | **Primary outcome**<br>• Unconjugated bilirubin 36 hours after starting phototherapy<br>No other outcomes prespecified or reported |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: [sic] "We divide 300 patients into two equal groups (group A and group B) 150 patients in each group. Name of all patients were written on paper slips and each slip was coded was coded with numbers (1-300). A blind person was asked to choose a slip from the box. First slips (even or odd) was included in |

**Khalid 2017** *(Continued)*

| | | |
|---|---|---|
| | | group A and remaining all patients were divided on the basis of that first slip (even or odd)." |
| Allocation concealment (selection bias) | Low risk | Quote [sic] "We divide 300 patients into two equal groups (group A and group B) 150 patients in each group. Name of all patients were written on paper slips and each slip was coded was coded with numbers (1-300). A blind person was asked to choose a slip from the box. First slips (even or odd) was included in group A and remaining all patients were divided on the basis of that first slip (even or odd)." |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete outcome data provided for all infants |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| Other bias | Low risk | No other potential sources of bias were identified. |

**Lau 1984**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Single-centre, randomised controlled trial conducted in Hong Kong |
| Participants | **Inclusion criteria:** (quote:) "Jaundiced term infants"; birthweight ≥ 2.5 kg; serum bilirubin concentration 190 to 205 umol/L (11.5 to 12 mg/dL)<br>**Exclusion criteria:** jaundice of known causes |
| Interventions | Total N = 34<br>**Group A (n = 13):** continuous phototherapy<br>**Group B (n = 9):** intermittent phototherapy (4 hours on, 4 hours off)<br>**Group C (n = 12):** intermittent phototherapy (1 hour on, 3 hours off)<br>Phototherapy was stopped when serum bilirubin concentration 170 umol/L (10 mg/dL) |
| Outcomes | **Primary and secondary outcomes**<br>• Not specified<br>**Reported outcomes** |

**Lau 1984** *(Continued)*

- Peak serum bilirubin
- Rise in serum bilirubin
- Rate of increase in serum bilirubin
- Rate of decline in serum bilirubin
- Time to peak serum bilirubin
- Total duration of phototherapy
- Duration of actual exposure
- Total irradiation

| Notes | |
|---|---|

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation not described ((quote:) "the babies were randomised into one of three groups receiving different regimens of phototherapy"). |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment not described ((quote:) "the babies were randomised into one of three groups receiving different regimens of phototherapy"). |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete outcome data provided for all infants |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| Other bias | Low risk | No other potential sources of bias were identified. |

**Maurer 1973**

***Study characteristics***

| Methods | Single-centre, randomised controlled trial conducted in USA |
|---|---|
| Participants | **Inclusion criteria:** infants < 2500 grams; postnatal age < 24 hours<br>**Exclusion criteria:** positive Coombs' tests; potential ABO incompatibility; sepsis |
| Interventions | Total N = 69<br>**Group 1 (n = 17):** 125 mg of agar given with feeds every 3 hours for 4 days beginning at 18 hours |

**Maurer 1973** *(Continued)*

| | |
|---|---|
| | **Group 2 (n = 18):** intermittent phototherapy (12 hours daily for 4 days)<br>**Group 3 (n = 19):** continuous phototherapy (4 days)<br>**Group 4 (n = 15):** no intervention |
| Outcomes | **Primary and secondary outcomes**<br>• Not specified<br>**Reported outcomes**<br>• Daily serum bilirubin concentrations for 6 days |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation not described ((quote:) "infants ... were randomly assigned to one of four groups"). |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment not described ((quote:) "infants ... were randomly assigned to one of four groups"). |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Completeness of data not specified |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| Other bias | Low risk | No other potential sources of bias were identified. |

**Niknafs 2008**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Single-centre, randomised controlled trial conducted in Iran |
| Participants | **Inclusion criteria:** infants with unconjugated jaundice; weight > 2000 grams |

**Niknafs 2008** *(Continued)*

| | |
|---|---|
| | **Exclusion criteria:** (quote:) "Concomitant diseases"; hyperbilirubinaemia, (quote:) "exceeding the range of exchange transfusion" or (quote:) "requiring high intensity phototherapy" |
| Interventions | Total N = 114<br>**Group I (n = 57):** continuous phototherapy (2 hours on, 30 minutes off)<br>**Group II (n = 57):** intermittent phototherapy (1 hour on, 1 hour off)<br>All infants received at least 24 hours phototherapy (criteria for stopping not specified). |
| Outcomes | **Primary and secondary outcomes**<br>• Not specified<br>**Reported outcomes**<br>• Total serum bilirubin after 12, 24, 26 and 48 hours of phototherapy<br>• Decrease in total serum bilirubin after 24 hours of phototherapy |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation not described ((quote:) "neonates ... were randomly divided into two groups"). |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment not described ((quote:) "neonates ... were randomly divided into two groups"). |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete outcome data provided for all infants |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| Other bias | Low risk | No other potential sources of bias were identified. |

**Patil 2020**

***Study characteristics***

**Patil 2020** *(Continued)*

| | |
|---|---|
| Methods | Single-centre, randomised controlled trial conducted in India |
| Participants | **Inclusion criteria:** > 34 weeks gestation; birth weight ≥ 2500 grams; 1 min APGAR score > 7<br><br>**Exclusion criteria:** rhesus incompatibility; ABO incompatibility; neonatal sepsis; congenital malformation; ((quote:) "preterms"); ((quote:) "low birth weights") |
| Interventions | Total N= 190<br><br>**Group 1 (n = 92):** continuous phototherapy (3 hours on, 45 minutes off)<br><br>**Group 2 (n = 98):** intermittent phototherapy (3 hours on, 3 hours off)<br><br>All infants received phototherapy for 48 hours. Criteria for initiation of phototherapy "as per American Academy of Paediatrics 2004 guidelines" |
| Outcomes | Primary outcome<br><br>• Not specified<br><br>Reported outcomes<br><br>• Rate of fall of bilirubin<br>• Decrease in total serum bilirubin<br>• Duration of phototherapy<br>• Duration of hospitalisation |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomisation was done using block randomisation (block size 10) in which 190 subjects were equally grouped". |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment not described |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete outcome data provided for all infants |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |

**Patil 2020** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | No other potential sources of bias were identified. |

**Romagnoli 1976**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Single-centre, randomised controlled trial conducted in Italy |
| Participants | **Inclusion criteria:** quote: "Preterm newborn infants" (gestation not specified)<br>**Exclusion criteria:** severe respiratory disease; haemolytic conditions; septic conditions; malformation |
| Interventions | Total N = 90<br>**Group I (n = 31):** no intervention (exchange transfusion if required)<br>**Group II (n = 31):** continuous phototherapy (started day 1 of life, stopped day 5 of life (average 96 hours))<br>**Group III (n = 28):** intermittent phototherapy (12 hours on, 12 hours off; started day of life, stopped day 7 of life (total 72 hours of phototherapy)) |
| Outcomes | **Primary outcome**<br>• (quote:) "Somatic development during the first four weeks of life"<br>**Reported outcomes**<br>• Daily bilirubin level for first 7 days of life<br>• Bilirubin level > 12 mg/dL<br>• Bilirubin level > 15 mg/dL<br>• Exchange transfusion<br>• Weekly weight and head circumference for first 4 weeks of life |
| Notes | Article in Italian |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation not described ((quote:) "Subjects included in the study were assigned 'randomly' to one of the three study groups"). |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment not described ((quote:) "Subjects included in the study were assigned 'randomly' to one of the three study groups"). |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias) | Low risk | Unblinded study with objective outcome measures |

**Romagnoli 1976** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Completeness of data not specified |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| Other bias | Low risk | No other potential sources of bias were identified. |

**Sachdeva 2015**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Single-centre, randomised controlled trial conducted in India |
| Participants | **Inclusion criteria:** (quote:) "Healthy" infants > 34 weeks' gestation; hyperbilirubinaemia requiring phototherapy for a minimum of 8 hours<br><br>**Exclusion criteria:** (quote:) "Major congenital malformations"; Apgar score < 4 at 5 minutes; onset of jaundice within first 24 hours of life, total serum bilirubin > 18 mg/dL at the time of admission; rise of bilirubin > 0.5 mg/dL/h in the initial 8 hours of starting phototherapy; haemolytic cause of jaundice (positive Coombs' test, evidence of haemolysis on peripheral smear, reticulocyte count > 6%); total serum bilirubin in exchange range at the time of admission; requiring NICU admission for any reason other than jaundice; direct bilirubin > 15% of total bilirubin; direct bilirubin > 1.5 mg/dL |
| Interventions | Total N = 75<br><br>**Group 1 (n = 39):** continuous phototherapy (phototherapy interrupted for feeding)<br><br>**Group 2 (n = 36):** intermittent phototherapy (12 hours on, 12 hours off)<br><br>Phototherapy was continued until 2 serum bilirubin values measured 12 hours apart < 13 mg/dL |
| Outcomes | **Primary outcome**<br><br>• Rate of fall of bilirubin (difference between maximum bilirubin after enrolment and bilirubin at end of phototherapy divided by the duration of phototherapy (actual duration of exposure))<br><br>**Secondary outcomes**<br><br>• Duration of phototherapy<br>• Failure of phototherapy<br>• Incidence of rebound phototherapy (2nd episode of hyperbilirubinaemia requiring phototherapy)<br>• Duration of hospitalisation |
| Notes | CTRI registration number: CTRI/2014/05/004584 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "the infant was randomized either into intermittent (IPT) or continuous (CPT) group using a computer-generated random number sequence with 1:1 allocation ratio". |

**Sachdeva 2015** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Quote: "The site investigator allocated the group by opening serially numbered, opaque, sealed, identical envelopes containing the treatment group allocation". |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Unblinded study with objective outcome measures |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Complete outcome data provided for all infants |
| Selective reporting (reporting bias) | Unclear risk | Trial registered retrospectively |
| Other bias | Low risk | No other potential sources of bias were identified |

**Taheritafti 2019**

| ***Study characteristics*** | |
|---|---|
| Methods | Single-centre, randomised controlled trial conducted in Iran |
| Participants | **Inclusion criteria:** term infants (gestational age ≥ 37 weeks); (quote:) "non-haemolytic hyperbilirubinaemia"<br><br>**Exclusion criteria:** haemolytic anaemia; prematurity; sepsis; severe hyperbilirubinaemia (total bilirubin > 18 mg/dL); conjugated hyperbilirubinaemia; onset of jaundice within first 24 hours of life |
| Interventions | Total N = 60<br><br>**Group 1 (n = 30):** continuous phototherapy<br><br>**Group 2 (n = 30):** intermittent phototherapy (18 hours on, 8 hours off)<br><br>Phototherapy was continued until total serum bilirubin < 11 mg/dL (breaks up to 1 hour allowed during breastfeeding, changing and changing of diapers (both groups)) |
| Outcomes | **Primary outcomes**<br><br>• Total bilirubin after 6 hours of phototherapy<br>• Melatonin levels<br><br>**Secondary outcomes**<br><br>• Kernicterus<br>• Complications<br>• Duration of phototherapy |

**Taheritafti 2019** *(Continued)*

| | |
|---|---|
| | • Length of hospital stay<br><br>**Other reported outcomes**<br><br>• Total bilirubin after 24 hours of phototherapy<br>• Total bilirubin after 36 hours of phototherapy |
| Notes | IRCT registration number: **IRCT2015112225184N1** |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "neonates via block randomization were divided into two groups". |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment not described |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Unblinded study with objective outcome measures |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Complete outcome data provided for all infants |
| Selective reporting (reporting bias) | High risk | Reported bilirubin levels at different time points to prespecified time points in trial registry; trial registered during recruitment phase |
| Other bias | Low risk | No other potential sources of bias were identified. |

**Wu 1974**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Single-centre, randomised controlled trial conducted in USA |
| Participants | **Inclusion criteria:** (quote:) "Preterm infants"; birthweight 1250 to 2000 grams<br><br>**Exclusion criteria:** (quote:) "Gross congenital anomalies"; haemolytic anemias; severe respiratory distress syndrome |
| Interventions | Total N = 120<br><br>**Group I (n = 40):** no intervention<br><br>**Group II (n = 40):** continuous phototherapy |

**Wu 1974** *(Continued)*

| | |
|---|---|
| | **Group III (n = 40):** intermittent phototherapy (12 hours on, 12 hours off)<br>Phototherapy started at 24 to 48 hours of life and continued for 5 days |
| Outcomes | **Primary and secondary outcomes**<br>• Not specified<br>**Reported outcomes**<br>• Daily mean serum bilirubin levels<br>• Number of infants with bilirubin levels > 12 mg/dL<br>• Number of infants with bilirubin levels > 15 mg/dL<br>• Daily mean blood glucose levels<br>• Weekly weight, length and head circumference for first 4 weeks of life |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation not described in sufficient detail (quote:) "Assignment of infants to the different groups was by randomized cards". |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment not described (quote:) "Assignment of infants to the different groups was by randomized cards". |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Unblinded study with objective outcome measures |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete outcome data provided for all infants |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| Other bias | Low risk | No other potential sources of bias were identified. |

**CPT**: continuous phototherapy
**CTRI**: Clinical Trials Registry India
**IPT**: intermittent phototherapy
**IRCT**: Iranian Registry of Clinical Trials
**NICU:** neonatal intensive care unit
**PT:** phototherapy

**Characteristics of excluded studies** *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Broughton 1965 | Compared phototherapy to no phototherapy. Groups not different with respect to intermittent versus continuous phototherapy |
| Bryla 1985 | Compared phototherapy to no phototherapy. Groups not different with respect to intermittent versus continuous phototherapy |
| Elliot 1974 | Compared phototherapy to no phototherapy. Groups not different with respect to intermittent versus continuous phototherapy |
| Goudarzvand 2019 | Compared Kangaroo mother care with no Kangaroo mother care during phototherapy. Groups not different with respect to intermittent versus continuous phototherapy |
| Hodgman 1970 | Compared phototherapy to no phototherapy. Groups not different with respect to intermittent versus continuous phototherapy |
| Komar-Szymborska 1994 | Retrospective cohort study |
| Krueger Jr 2001 | Compared two different phototherapy units. Groups not different with respect to intermittent versus continuous phototherapy |
| Ludington-Hoe 2001 | Compared Kangaroo mother care with no Kangaroo mother care during phototherapy. Groups not different with respect to intermittent versus continuous phototherapy |
| Martinez 1992 | Compared breastfeeding to no breastfeeding and phototherapy to no phototherapy. Groups not different with respect to intermittent versus continuous phototherapy |
| Morris 2008 | Compared different thresholds for commencement of phototherapy. Groups not different with respect to intermittent versus continuous phototherapy |
| Namnabati 2019 | Compared home-based phototherapy with hospital-based phototherapy. Groups not different with respect to intermittent versus continuous phototherapy |
| Tabb 1972 | Compared different durations of phototherapy. Groups not different with respect to intermittent versus continuous phototherapy |
| Vogl 1978 | Non-randomised controlled trial comparing continuous phototherapy with three different intermittent phototherapy regimens |
| Woodall 1992 | Compared two different phototherapy units. Groups not different with respect to<br>intermittent versus continuous phototherapy |
| Yilmaz 2015 | Compared 2 different phototherapy units. Groups not different with respect to intermittent versus continuous phototherapy |
| Zainab 2004 | Non-randomised study comparing home-based phototherapy with hospital-based phototherapy |

**Characteristics of studies awaiting classification** *[ordered by study ID]*

**CTRI/2012/09/002968**

| | |
|---|---|
| Methods | Single-centre, randomised controlled trial conducted in India |

**CTRI/2012/09/002968** *(Continued)*

| | |
|---|---|
| Participants | **Inclusion criteria:** ((quote:) "Babies who were born at a gestation of ≥ 35 weeks and developed jaundice, with bilirubin cutoffs, requiring phototherapy within first two weeks of life, as per AAP practice parameter guidelines will be included in the study if parents are willing to give informed written consent").<br><br>**Exclusion criteria:** ((quote:) "Babies with haemolytic jaundice – Rh, ABO, or minor group incompatibility with DCT positive or other haemolytic conditions like G6PD deficiency or peripheral smear showing haemolysis"); ((quote "Total serum bilirubin levels 20 mg/dL"); ((quote "Sepsis (symptomatic screen positive/culture positive)"); ((quote "Babies who have received prior phototherapy"); ((quote "Babies with hydrops fetalis or major congenital malformations") |
| Interventions | Total N = 110<br><br>**Group A:** continuous phototherapy<br><br>**Group B:** intermittent phototherapy (2 hours on, 2 hours off)<br><br>Duration of phototherapy and criteria for stopping not specified |
| Outcomes | **Primary outcome**<br><br>• ((quote:) "rate of fall of bilirubin defined as difference between total serum bilirubin (TSB) at onset and at termination of phototherapy divided by duration of phototherapy")<br><br>**Secondary outcomes**<br><br>• Duration of phototherapy<br>• Failure of phototherapy and need for exchange transfusion<br>• Need for phototherapy for rebound increase in bilirubin<br>• Incidence of hyperthermia 38°C<br>• Maternal perception of satisfaction of care and feeding<br>• Breastfeeding assessment at discharge |
| Notes | Retrospectively registered<br><br>Results not reported |

**IRCT201012255459N1**

| | |
|---|---|
| Methods | Single-centre, randomised controlled trial conducted in Iran |
| Participants | **Inclusion criteria:** ((quote:) "neonate between 2-14 day old, body weight more than 2500 grams"); ((quote:) "absence of other concomitant diseases"); ((quote:) "bilirubin between 16 mg/dL and 22 mg/dL"); ((quote:) "obtaining approval letter from the ethics committee)")<br><br>**Exclusion criteria:** ((quote:) "body weight under 2500 grams"); ((quote:) "presence of any concomitant diseases"); ((quote:) "need to blood exchange"); ((quote:) "need to intensive phototherapy"); ((quote:) "gestational age lower than 37 weeks"); ((quote:) "prolonged icterus (more than 14 day)"); ((quote:) "direct bilirubin more than 2 mg/dL") |
| Interventions | Total N = 96<br><br>**Group A:** continuous phototherapy (2 hours on, 0.5 hours off)<br><br>**Group B:** intermittent phototherapy (1 hour on, 1 hour off)<br><br>All infants received 48 hours phototherapy. |
| Outcomes | **Primary outcome** |

**IRCT201012255459N1** *(Continued)*

| | |
|---|---|
| | • Indirect bilirubin (12, 24, 36, 48 hours after beginning of phototherapy) |
| Notes | Retrospectively registered, recruitment status "complete"<br><br>Results not reported |

**Khaliq 2016**

| | |
|---|---|
| Methods | Single-centre, randomised controlled trial conducted in Pakistan |
| Participants | **Inclusion criteria:** infants ≥ 37 weeks' gestation; postnatal age > 24 hours to ≤ 10 days and unconjugated bilirubin 12 to 20 mg/dL; APGAR > 6 at 5 minutes<br><br>**Exclusion criteria:** infants requiring intensive care ((quote:) "i.e. ventilator, endotracheal intubation, and peritoneal dialysis"); major congenital malformation ((quote:) "cardiac, skeletal, renal, dysmorphism etc"); sepsis ((quote:) "i.e. positive blood culture, fits, reluctance to feed, platelets < 50000") |
| Interventions | Total N = 258<br><br>**Group A (n = 129):** continuous phototherapy (2 hours on, 20 minutes off)<br><br>**Group B (n = 129):** intermittent phototherapy (1 hour on, 30 minutes off)<br><br>Duration of phototherapy and criteria for stopping not specified |
| Outcomes | **Primary outcome**<br><br>• Mean decrease in serum bilirubin 36 hours after commencing phototherapy |
| Notes | Reported results identical to Suri 2019 (awaiting response from respective authors and editors) |

**Suri 2019**

| | |
|---|---|
| Methods | Single-centre, randomised controlled trial conducted in India |
| Participants | **Inclusion criteria:** infants ≥ 37 weeks' gestation; postnatal age > 24 hours to ≤ 10 days and unconjugated bilirubin 12 to 20 mg/dL; APGAR > 6 at 5 minutes<br><br>**Exclusion criteria:** infants requiring intensive care ((quote:) "i.e. ventilator, endotracheal intubation, and peritoneal dialysis"); major congenital malformation ((quote:) "cardiac, skeletal, renal, dysmorphism etc"); sepsis ((quote:) "i.e. positive blood culture, fits, reluctance to feed, platelets < 50000"); (quote:) "congenital abnormalities"; (quote:) "Mothers those who are not willing" |
| Interventions | Total N variably reported (N = 100; N = 258)<br><br>**Group A (n variably reported (n = 50; n = 129)):** continuous phototherapy (2 hours on, 20 minutes off)<br><br>**Group B (n variably reported (n = 50; n = 129)):** intermittent phototherapy (1 hour on, 30 minutes off)<br><br>Duration of phototherapy and criteria for stopping not specified |
| Outcomes | **Primary outcome** |

| | |
|---|---|
| **Suri 2019** *(Continued)* | • Serum bilirubin 36 hours after commencing phototherapy |
| Notes | Reported results identical to Khaliq 2016 (awaiting response from respective authors and editors) |

AAP: American Academy of Pediatrics
DCT: Direct Coombs Test
G6PD: glucose-6-phosphate dehydrogenase
Rh: rhesus
TSB: total serum bilirubin

## Characteristics of ongoing studies *[ordered by study ID]*

### NCT03927833

| | |
|---|---|
| Study name | Cycled phototherapy: a safer effective method to control the serum bilirubin of extremely premature infants? |
| Methods | Multicentre randomised controlled trial conducted in USA |
| Participants | **Inclusion criteria:** inborn infants; ≤ 750 grams at birth and/or < 27 weeks' gestation at birth; 12 to 36 hours of age<br><br>**Exclusion criteria:** unable to enrol infant by 36 hours of age; previous phototherapy; known haemolytic disease; TSB reported as > 6.0 mg/dL before 12 hours age; major anomaly; overt non-bacterial infection; infant unlikely to survive |
| Interventions | Total N = 1700<br><br>**Group 1:** cycled phototherapy at timed intervals, dependent upon total serum bilirubin (TSB) levels (cycled phototherapy begins with > 15 minutes per hour cycled PT regimen and increased to 30 minutes per hour if the TSB is 8.0 to 9.9 and 60 minutes per hour if the TSB is > 10 mg/dL)<br><br>**Group 2:** continuous phototherapy |
| Outcomes | **Primary outcome**<br><br>• Survival to discharge<br><br>**Secondary outcomes**<br><br>• Number of hours of phototherapy<br>• Number of irradiance hours<br>• Peak concentration of total serum bilirubin<br>• Concentration of total serum bilirubin<br>• Major neonatal morbidity; severe ICH<br>• Ventricular enlargement of cystic white matter disease<br>• Bronchopulmonary dysplasia<br>• Late onset sepsis<br>• Necrotising enterocolitis<br>• Grade 3 (or greater) retinopathy of prematurity<br>• Patent ductus arteriosus treated with surgery or NSAIDS<br>• Neurodevelopmental impairment<br>• Neurodevelopmental impairment or death |
| Starting date | 2020 |
| Contact information | Jon Tyson; email: Jon.E.Tyson@uth.tmc.edu |

| | |
|---|---|
| **NCT03927833** *(Continued)* | |
| | NICHD Neonatal Research Network |
| Notes | |

**ICH:** intracranial haemorrhage
**NICHD:** National Institute of Child Health and Human Development
**NSAIDS:** nonsteroidal anti-inflammatory drugs
**PT:** phototherapy
**TSB:** total serum bilirubin

## DATA AND ANALYSES

### Comparison 1. Intermittent phototherapy versus continuous phototherapy

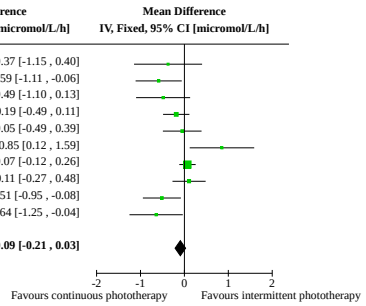
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 Rate of decline of serum bilirubin | 10 | 1225 | Mean Difference (IV, Fixed, 95% CI) | -0.09 [-0.21, 0.03] |
| 1.2 BIND | 1 | 60 | Odds Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 1.3 Treatment failure | 1 | 75 | Risk Difference (IV, Fixed, 95% CI) | 0.03 [-0.08, 0.15] |
| 1.4 Mortality | 10 | 1470 | Risk Difference (M-H, Fixed, 95% CI) | -0.01 [-0.03, 0.01] |
| 1.5 Exchange transfusion | 2 | 364 | Risk Difference (M-H, Fixed, 95% CI) | 0.00 [-0.02, 0.02] |
| 1.6 Weight gain (g/kg/day) | 1 | 59 | Mean Difference (IV, Fixed, 95% CI) | -3.71 [-10.25, 2.82] |
| 1.7 Length of hospital stay | 3 | 325 | Mean Difference (IV, Fixed, 95% CI) | -0.07 [-0.22, 0.09] |
| 1.8 Infant feeding volumes (volume/day) | 2 | 136 | Mean Difference (IV, Fixed, 95% CI) | -0.82 [-8.80, 7.16] |
| 1.9 Duration of phototherapy (hours) | 7 | 917 | Mean Difference (IV, Fixed, 95% CI) | -15.27 [-16.42, -14.12] |
| 1.10 Duration of first episode of phototherapy | 6 | 629 | Mean Difference (IV, Fixed, 95% CI) | -0.89 [-2.50, 0.72] |
| 1.11 Parental satisfaction | 1 | 174 | Mean Difference (IV, Fixed, 95% CI) | 2.00 [1.56, 2.44] |
| 1.12 Staff satisfaction | 1 | 174 | Mean Difference (IV, Fixed, 95% CI) | -2.00 [-2.35, -1.65] |
| 1.13 Incidence of gastrointestinal dysmotility | 1 | 174 | Risk Difference (M-H, Fixed, 95% CI) | -0.01 [-0.06, 0.04] |
| 1.14 Incidence of patent ductus arteriosus | 1 | 271 | Risk Difference (M-H, Fixed, 95% CI) | -0.02 [-0.12, 0.08] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.15 Incidence of body rash | 1 | 174 | Risk Difference (M-H, Fixed, 95% CI) | -0.01 [-0.07, 0.05] |

## Analysis 1.1. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 1: Rate of decline of serum bilirubin

| Study or Subgroup | Intermittent Phototherapy Mean [micromol/L/h] | SD [micromol/L/h] | Total | Continuous Phototherapy Mean [micromol/L/h] | SD [micromol/L/h] | Total | Weight | Mean Difference IV, Fixed, 95% CI [micromol/L/h] |
|---|---|---|---|---|---|---|---|---|
| Maurer 1973 | -1.472 | 1.294 | 18 | -1.1 | 1.096 | 19 | 2.4% | -0.37 [-1.15 , 0.40] |
| Wu 1974 | -0.383 | 1.294 | 40 | 0.203 | 1.096 | 40 | 5.2% | -0.59 [-1.11 , -0.06] |
| Romagnoli 1976 | -2.072 | 1.294 | 28 | -1.587 | 1.096 | 31 | 3.8% | -0.49 [-1.10 , 0.13] |
| Caldera 1984 | 1.793 | 0.983 | 103 | 1.979 | 0.983 | 69 | 15.9% | -0.19 [-0.49 , 0.11] |
| Niknafs 2008 | 3.897 | 1.294 | 57 | 3.947 | 1.096 | 57 | 7.4% | -0.05 [-0.49 , 0.39] |
| Sachdeva 2015 | 3.078 | 2.027 | 36 | 2.223 | 1.013 | 39 | 2.6% | 0.85 [0.12 , 1.59] |
| Khalid 2017 | 0.066 | 0.774 | 150 | -0.004 | 0.869 | 150 | 41.2% | 0.07 [-0.12 , 0.26] |
| Patil 2020 | 3.555 | 1.294 | 83 | 3.449 | 1.096 | 71 | 10.0% | 0.11 [-0.27 , 0.48] |
| Gottimukkala 2021 | 2.223 | 1.393 | 85 | 2.736 | 1.52 | 89 | 7.6% | -0.51 [-0.95 , -0.08] |
| Taheritafti 2019 | 1.978 | 1.294 | 30 | 2.622 | 1.096 | 30 | 3.9% | -0.64 [-1.25 , -0.04] |
| **Total (95% CI)** | | | **630** | | | **595** | **100.0%** | **-0.09 [-0.21 , 0.03]** |

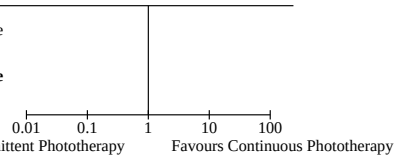
Heterogeneity: Chi² = 23.04, df = 9 (P = 0.006); I² = 61%
Test for overall effect: Z = 1.52 (P = 0.13)
Test for subgroup differences: Not applicable




## Analysis 1.2. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 2: BIND

| Study or Subgroup | Intermittent phototherapy Events | Total | Continuous phototherapy Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Taheritafti 2019 | 0 | 30 | 0 | 30 | | Not estimable |
| **Total (95% CI)** | | **30** | | **30** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |

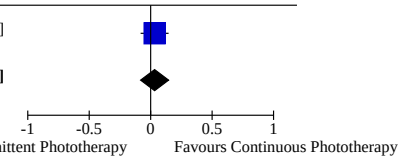
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable




## Analysis 1.3. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 3: Treatment failure

| Study or Subgroup | Intermittent phototherapy Events | Total | Continuous phototherapy Events | Total | Weight | Risk Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Sachdeva 2015 | 3 | 36 | 2 | 39 | 100.0% | 0.03 [-0.08 , 0.15] |
| **Total (95% CI)** | | **36** | | **39** | **100.0%** | **0.03 [-0.08 , 0.15]** |
| Total events: | 3 | | 2 | | | |

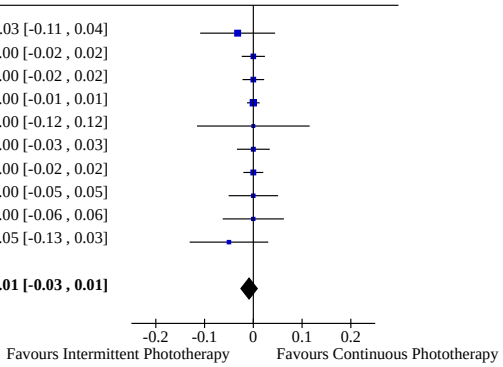
Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable



## Analysis 1.4. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 4: Mortality

| Study or Subgroup | Intermittent phototherapy Events | Total | Continuous phototherapy Events | Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Arnold 2020 | 14 | 137 | 18 | 134 | 18.5% | -0.03 [-0.11 , 0.04] |
| Caldera 1984 | 0 | 103 | 0 | 69 | 11.3% | 0.00 [-0.02 , 0.02] |
| Gottimukkala 2021 | 0 | 85 | 0 | 89 | 11.9% | 0.00 [-0.02 , 0.02] |
| Khalid 2017 | 0 | 150 | 0 | 150 | 20.5% | 0.00 [-0.01 , 0.01] |
| Lau 1984 | 0 | 21 | 0 | 13 | 2.2% | 0.00 [-0.12 , 0.12] |
| Niknafs 2008 | 0 | 57 | 0 | 57 | 7.8% | 0.00 [-0.03 , 0.03] |
| Patil 2020 | 0 | 98 | 0 | 92 | 13.0% | 0.00 [-0.02 , 0.02] |
| Sachdeva 2015 | 0 | 36 | 0 | 39 | 5.1% | 0.00 [-0.05 , 0.05] |
| Taheritafti 2019 | 0 | 30 | 0 | 30 | 4.1% | 0.00 [-0.06 , 0.06] |
| Wu 1974 | 0 | 40 | 2 | 40 | 5.5% | -0.05 [-0.13 , 0.03] |
| **Total (95% CI)** | | **757** | | **713** | **100.0%** | **-0.01 [-0.03 , 0.01]** |
| Total events: | 14 | | 20 | | | |

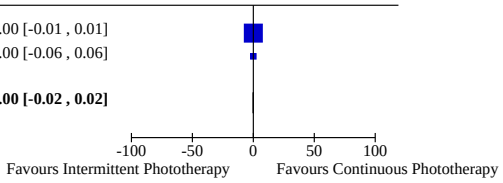
Heterogeneity: Chi² = 5.36, df = 9 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable




## Analysis 1.5. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 5: Exchange transfusion

| Study or Subgroup | Intermittent phototherapy Events | Total | Continuous phototherapy Events | Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Arnold 2020 | 0 | 171 | 0 | 134 | 83.6% | 0.00 [-0.01 , 0.01] |
| Romagnoli 1976 | 0 | 28 | 0 | 31 | 16.4% | 0.00 [-0.06 , 0.06] |
| **Total (95% CI)** | | **199** | | **165** | **100.0%** | **0.00 [-0.02 , 0.02]** |
| Total events: | 0 | | 0 | | | |

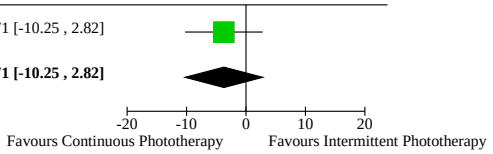
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable




## Analysis 1.6. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 6: Weight gain (g/kg/day)

| Study or Subgroup | Intermittent phototherapy Mean | SD | Total | Continuous phototherapy Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Romagnoli 1976 | -10.714 | 12.71 | 28 | -7 | 12.86 | 31 | 100.0% | -3.71 [-10.25 , 2.82] |
| **Total (95% CI)** | | | **28** | | | **31** | **100.0%** | **-3.71 [-10.25 , 2.82]** |

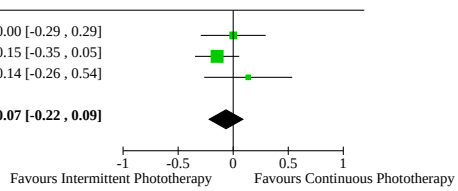
Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable




## Analysis 1.7. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 7: Length of hospital stay

| Study or Subgroup | Intermittent phototherapy Mean [days] | SD [days] | Total | Continuous phototherapy Mean [days] | SD [days] | Total | Weight | Mean Difference IV, Fixed, 95% CI [days] |
|---|---|---|---|---|---|---|---|---|
| Sachdeva 2015 | 1.375 | 0.479 | 36 | 1.375 | 0.796 | 39 | 27.0% | 0.00 [-0.29 , 0.29] |
| Patil 2020 | 1.354 | 0.708 | 98 | 1.5 | 0.701 | 92 | 58.3% | -0.15 [-0.35 , 0.05] |
| Taheritafti 2019 | 2.4667 | 0.937 | 30 | 2.33 | 0.606 | 30 | 14.7% | 0.14 [-0.26 , 0.54] |
| **Total (95% CI)** | | | **164** | | | **161** | **100.0%** | **-0.07 [-0.22 , 0.09]** |

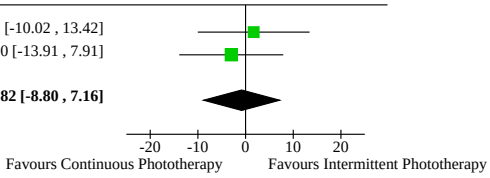
Heterogeneity: Chi² = 1.79, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.40)
Test for subgroup differences: Not applicable



## Analysis 1.8. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 8: Infant feeding volumes (volume/day)

| Study or Subgroup | Intermittent phototherapy Mean | SD | Total | Continuous phototherapy Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Romagnoli 1976 | 141.1 | 27.7 | 28 | 139.4 | 16.1 | 31 | 46.4% | 1.70 [-10.02 , 13.42] |
| Wu 1974 | 115 | 24.6 | 40 | 118 | 24.2 | 37 | 53.6% | -3.00 [-13.91 , 7.91] |
| **Total (95% CI)** | | | **68** | | | **68** | **100.0%** | **-0.82 [-8.80 , 7.16]** |

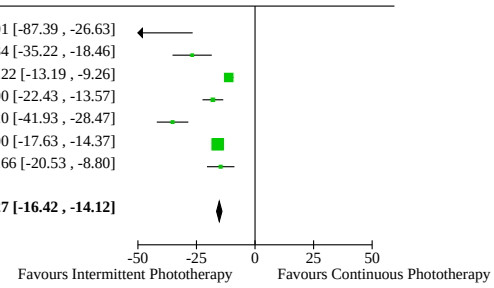
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable




## Analysis 1.9. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 9: Duration of phototherapy (hours)

| Study or Subgroup | Intermittent Phototherapy Mean | SD | Total | Continuous Phototherapy Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Lau 1984 | 32.886 | 17.318 | 21 | 89.9 | 54.2 | 13 | 0.1% | -57.01 [-87.39 , -26.63] |
| Caldera 1984 | 42.757 | 20.728 | 103 | 69.6 | 31.2 | 69 | 1.9% | -26.84 [-35.22 , -18.46] |
| Niknafs 2008 | 15.895 | 4.165 | 57 | 27.116 | 6.317 | 57 | 34.3% | -11.22 [-13.19 , -9.26] |
| Sachdeva 2015 | 12 | 4.444 | 36 | 30 | 13.333 | 39 | 6.8% | -18.00 [-22.43 , -13.57] |
| Arnold 2020 | 36.8 | 21.018 | 160 | 72 | 34 | 128 | 2.9% | -35.20 [-41.93 , -28.47] |
| Gottimukkala 2021 | 8 | 2.469 | 85 | 24 | 7.407 | 89 | 50.1% | -16.00 [-17.63 , -14.37] |
| Taheritafti 2019 | 31.339 | 11.351 | 30 | 46 | 11.826 | 30 | 3.9% | -14.66 [-20.53 , -8.80] |
| **Total (95% CI)** | | | **492** | | | **425** | **100.0%** | **-15.27 [-16.42 , -14.12]** |

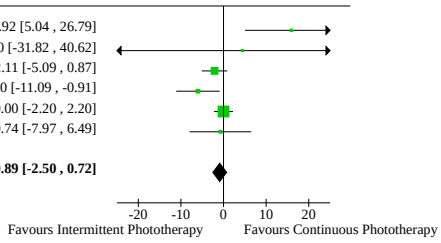
Heterogeneity: Chi² = 66.86, df = 6 (P < 0.00001); I² = 91%
Test for overall effect: Z = 26.00 (P < 0.00001)
Test for subgroup differences: Not applicable




## Analysis 1.10. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 10: Duration of first episode of phototherapy

| Study or Subgroup | Intermittent phototherapy Mean [hours] | SD [hours] | Total | Continuous phototherapy Mean [hours] | SD [hours] | Total | Weight | Mean Difference IV, Fixed, 95% CI [hours] |
|---|---|---|---|---|---|---|---|---|
| Caldera 1984 | 85.515 | 41.457 | 103 | 69.6 | 31.2 | 69 | 2.2% | 15.92 [5.04 , 26.79] |
| Lau 1984 | 94.3 | 49.256 | 21 | 89.9 | 54.2 | 13 | 0.2% | 4.40 [-31.82 , 40.62] |
| Niknafs 2008 | 31.789 | 8.33 | 57 | 33.895 | 7.896 | 57 | 29.2% | -2.11 [-5.09 , 0.87] |
| Sachdeva 2015 | 24 | 8.9 | 36 | 30 | 13.33 | 39 | 10.0% | -6.00 [-11.09 , -0.91] |
| Gottimukkala 2021 | 24 | 7.407 | 85 | 24 | 7.407 | 89 | 53.5% | 0.00 [-2.20 , 2.20] |
| Taheritafti 2019 | 45.26 | 16.396 | 30 | 46 | 11.826 | 30 | 5.0% | -0.74 [-7.97 , 6.49] |
| **Total (95% CI)** | | | **332** | | | **297** | **100.0%** | **-0.89 [-2.50 , 0.72]** |

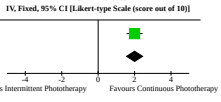
Heterogeneity: Chi² = 14.39, df = 5 (P = 0.01); I² = 65%
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable



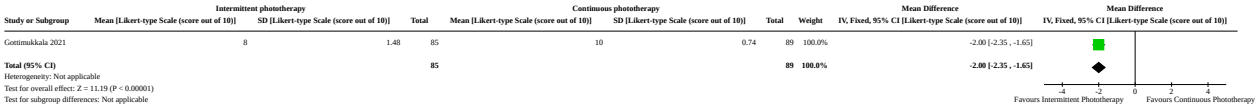

## Analysis 1.11. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 11: Parental satisfaction

| Study or Subgroup | Intermittent phototherapy Mean [Likert-type Scale (score out of 10)] | SD [Likert-type Scale (score out of 10)] | Total | Continuous phototherapy Mean [Likert-type Scale (score out of 10)] | SD [Likert-type Scale (score out of 10)] | Total | Weight | Mean Difference IV, Fixed, 95% CI [Likert-type Scale (score out of 10)] |
|---|---|---|---|---|---|---|---|---|
| Gottimukkala 2021 | 9 | 1.48 | 85 | 7 | 1.48 | 89 | 100.0% | 2.00 [1.56 , 2.44] |
| **Total (95% CI)** | | | **85** | | | **89** | **100.0%** | **2.00 [1.56 , 2.44]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 8.91 (P < 0.00001)
Test for subgroup differences: Not applicable



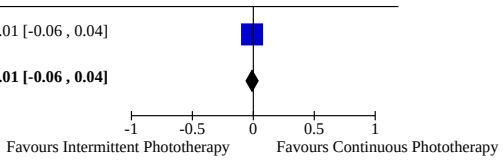
## Analysis 1.12. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 12: Staff satisfaction




## Analysis 1.13. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 13: Incidence of gastrointestinal dysmotility

| Study or Subgroup | Intermittent phototherapy Events | Total | Continuous phototherapy Events | Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Gottimukkala 2021 | 2 | 85 | 3 | 89 | 100.0% | -0.01 [-0.06 , 0.04] |
| **Total (95% CI)** | | **85** | | **89** | **100.0%** | **-0.01 [-0.06 , 0.04]** |
| Total events: | 2 | | 3 | | | |

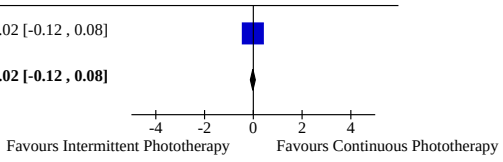
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable




## Analysis 1.14. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 14: Incidence of patent ductus arteriosus

| Study or Subgroup | Intermittent phototherapy Events | Total | Continuous phototherapy Events | Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Arnold 2020 | 31 | 137 | 33 | 134 | 100.0% | -0.02 [-0.12 , 0.08] |
| **Total (95% CI)** | | **137** | | **134** | **100.0%** | **-0.02 [-0.12 , 0.08]** |
| Total events: | 31 | | 33 | | | |

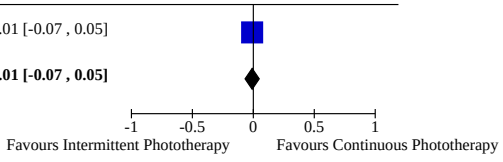
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Not applicable




## Analysis 1.15. Comparison 1: Intermittent phototherapy versus continuous phototherapy, Outcome 15: Incidence of body rash

| Study or Subgroup | Intermittent phototherapy Events | Total | Continuous phototherapy Events | Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Gottimukkala 2021 | 3 | 85 | 4 | 89 | 100.0% | -0.01 [-0.07 , 0.05] |
| **Total (95% CI)** | | **85** | | **89** | **100.0%** | **-0.01 [-0.07 , 0.05]** |
| Total events: | 3 | | 4 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable



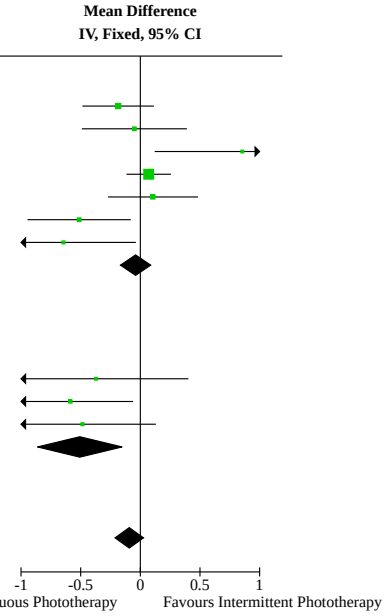

## Comparison 2. Intermittent phototherapy versus continuous phototherapy: subgrouped by term infants versus preterm infants

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 Rate of decline of serum bilirubin (micromol/L/hour) | 10 | 1225 | Mean Difference (IV, Fixed, 95% CI) | -0.09 [-0.21, 0.03] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1.1 Term infants | 7 | 1049 | Mean Difference (IV, Fixed, 95% CI) | -0.04 [-0.17, 0.09] |
| 2.1.2 Preterm infants | 3 | 176 | Mean Difference (IV, Fixed, 95% CI) | -0.51 [-0.86, -0.15] |
| 2.2 BIND | 1 | 60 | Odds Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 2.2.1 Term infants | 1 | 60 | Odds Ratio (M-H, Fixed, 95% CI) | Not estimable |

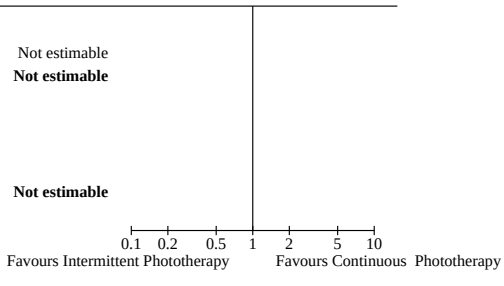
**Analysis 2.1. Comparison 2: Intermittent phototherapy versus continuous phototherapy: subgrouped by term infants versus preterm infants, Outcome 1: Rate of decline of serum bilirubin (micromol/L/hour)**

| Study or Subgroup | Intermittent phototherapy Mean | SD | Total | Continuous phototherapy Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.1.1 Term infants** | | | | | | | | |
| Caldera 1984 | 1.793 | 0.983 | 103 | 1.979 | 0.983 | 69 | 15.9% | -0.19 [-0.49 , 0.11] |
| Niknafs 2008 | 3.897 | 1.294 | 57 | 3.947 | 1.096 | 57 | 7.4% | -0.05 [-0.49 , 0.39] |
| Sachdeva 2015 | 3.078 | 2.027 | 36 | 2.223 | 1.013 | 39 | 2.6% | 0.85 [0.12 , 1.59] |
| Khalid 2017 | 0.066 | 0.774 | 150 | -0.004 | 0.869 | 150 | 41.2% | 0.07 [-0.12 , 0.26] |
| Patil 2020 | 3.555 | 1.294 | 83 | 3.449 | 1.096 | 71 | 10.0% | 0.11 [-0.27 , 0.48] |
| Gottimukkala 2021 | 2.223 | 1.393 | 85 | 2.736 | 1.52 | 89 | 7.6% | -0.51 [-0.95 , -0.08] |
| Taheritafti 2019 | 1.978 | 1.294 | 30 | 2.622 | 1.096 | 30 | 3.9% | -0.64 [-1.25 , -0.04] |
| **Subtotal (95% CI)** | | | **544** | | | **505** | **88.7%** | **-0.04 [-0.17 , 0.09]** |
| Heterogeneity: Chi² = 16.92, df = 6 (P = 0.010); I² = 65% | | | | | | | | |
| Test for overall effect: Z = 0.61 (P = 0.54) | | | | | | | | |
| **2.1.2 Preterm infants** | | | | | | | | |
| Maurer 1973 | -1.472 | 1.294 | 18 | -1.1 | 1.096 | 19 | 2.4% | -0.37 [-1.15 , 0.40] |
| Wu 1974 | -0.383 | 1.294 | 40 | 0.203 | 1.096 | 40 | 5.2% | -0.59 [-1.11 , -0.06] |
| Romagnoli 1976 | -2.072 | 1.294 | 28 | -1.587 | 1.096 | 31 | 3.8% | -0.49 [-1.10 , 0.13] |
| **Subtotal (95% CI)** | | | **86** | | | **90** | **11.3%** | **-0.51 [-0.86 , -0.15]** |
| Heterogeneity: Chi² = 0.21, df = 2 (P = 0.90); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 2.80 (P = 0.005) | | | | | | | | |
| **Total (95% CI)** | | | **630** | | | **595** | **100.0%** | **-0.09 [-0.21 , 0.03]** |
| Heterogeneity: Chi² = 23.04, df = 9 (P = 0.006); I² = 61% | | | | | | | | |
| Test for overall effect: Z = 1.52 (P = 0.13) | | | | | | | | |
| Test for subgroup differences: Chi² = 5.91, df = 1 (P = 0.02), I² = 83.1% | | | | | | | | |




**Analysis 2.2. Comparison 2: Intermittent phototherapy versus continuous phototherapy: subgrouped by term infants versus preterm infants, Outcome 2: BIND**

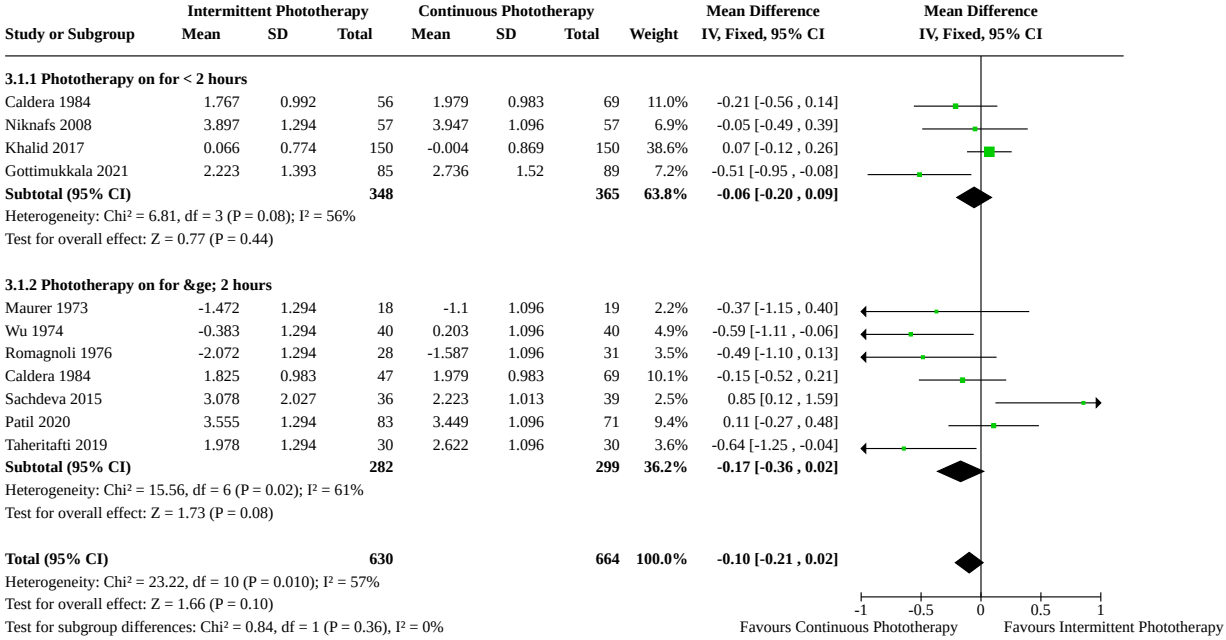
| Study or Subgroup | Intermittent phototherapy Events | Total | Continuous phototherapy Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.2.1 Term infants** | | | | | | |
| Taheritafti 2019 | 0 | 30 | 0 | 30 | | Not estimable |
| **Subtotal (95% CI)** | | **30** | | **30** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **Total (95% CI)** | | **30** | | **30** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



**Comparison 3. Intermittent phototherapy versus continuous phototherapy: subgrouped by intermittent phototherapy regimen (phototherapy on < 2 hours versus ≥ 2 hours)**

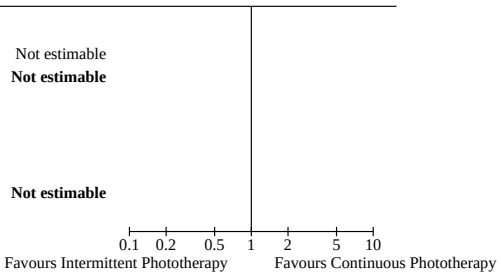
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.1 Rate of decline of serum bilirubin (micromol/L/hour) | 10 | 1294 | Mean Difference (IV, Fixed, 95% CI) | -0.10 [-0.21, 0.02] |
| 3.1.1 Phototherapy on for < 2 hours | 4 | 713 | Mean Difference (IV, Fixed, 95% CI) | -0.06 [-0.20, 0.09] |
| 3.1.2 Phototherapy on for ≥ 2 hours | 7 | 581 | Mean Difference (IV, Fixed, 95% CI) | -0.17 [-0.36, 0.02] |
| 3.2 BIND | 1 | 60 | Odds Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 3.2.1 Phototherapy on ≥2 hours | 1 | 60 | Odds Ratio (M-H, Fixed, 95% CI) | Not estimable |

**Analysis 3.1. Comparison 3: Intermittent phototherapy versus continuous phototherapy: subgrouped by intermittent phototherapy regimen (phototherapy on < 2 hours versus ≥ 2 hours), Outcome 1: Rate of decline of serum bilirubin (micromol/L/hour)**



### Analysis 3.2. Comparison 3: Intermittent phototherapy versus continuous phototherapy: subgrouped by intermittent phototherapy regimen (phototherapy on < 2 hours versus ≥ 2 hours), Outcome 2: BIND

| Study or Subgroup | Intermittent phototherapy Events | Total | Continuous phototherapy Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.2.1 Phototherapy on ≥2 hours** | | | | | | |
| Taheritafti 2019 | 0 | 30 | 0 | 30 | | Not estimable |
| **Subtotal (95% CI)** | | **30** | | **30** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **Total (95% CI)** | | **30** | | **30** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |

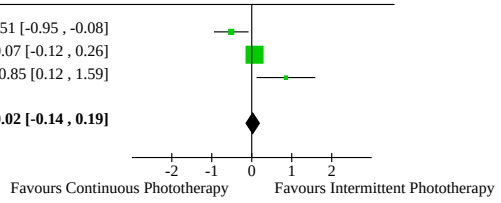



## Comparison 4. Sensitivity analysis

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.1 Rate of decline of bilirubin (micromol/L/hr) | 3 | 549 | Mean Difference (IV, Fixed, 95% CI) | 0.02 [-0.14, 0.19] |

### Analysis 4.1. Comparison 4: Sensitivity analysis, Outcome 1: Rate of decline of bilirubin (micromol/L/hr)

| Study or Subgroup | Intermittent phototherapy Mean | SD | Total | Continuous phototherapy Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Gottimukkala 2021 | 2.223 | 1.393 | 85 | 2.736 | 1.52 | 89 | 14.8% | -0.51 [-0.95 , -0.08] |
| Khalid 2017 | 0.066 | 0.774 | 150 | -0.004 | 0.869 | 150 | 80.0% | 0.07 [-0.12 , 0.26] |
| Sachdeva 2015 | 3.078 | 2.027 | 36 | 2.223 | 1.013 | 39 | 5.1% | 0.85 [0.12 , 1.59] |
| **Total (95% CI)** | | | **271** | | | **278** | **100.0%** | **0.02 [-0.14 , 0.19]** |
| Heterogeneity: Chi² = 11.06, df = 2 (P = 0.004); I² = 82% | | | | | | | | |
| Test for overall effect: Z = 0.28 (P = 0.78) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |




# APPENDICES

## Appendix 1. Cochrane CENTRAL strategy

Cochrane CENTRAL via CRS Web

January 31, 2022

| | | |
|---|---|---|
| 1 | MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET | 17409 |
| 2 | infant or infants or infant's or "infant s" or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU AND CENTRAL:TARGET | 95692 |

*(Continued)*

| | | |
|---|---|---|
| 3 | preemie OR preemies or pre-mature or pre-matures or pre-maturity AND CENTRAL:TARGET | 54 |
| 4 | #1 OR #2 OR #3 | 95701 |
| 5 | MESH DESCRIPTOR Hyperbilirubinemia EXPLODE ALL AND CENTRAL:TARGET | 636 |
| 6 | MESH DESCRIPTOR Hyperbilirubinemia, Neonatal EXPLODE ALL AND CENTRAL:TARGET | 360 |
| 7 | MESH DESCRIPTOR Jaundice, Neonatal EXPLODE ALL AND CENTRAL:TARGET | 270 |
| 8 | MESH DESCRIPTOR jaundice EXPLODE ALL AND CENTRAL:TARGET | 198 |
| 9 | MESH DESCRIPTOR Jaundice, Obstructive EXPLODE ALL AND CENTRAL:TARGET | 81 |
| 10 | MESH DESCRIPTOR kernicterus EXPLODE ALL AND CENTRAL:TARGET | 11 |
| 11 | hyperbilirubinemi* OR hyperbilirubinaemi* OR bilirubinemi* OR bilirubinaemi* OR jaundice OR jaundices OR jaundiced OR kernicterus OR icter* OR (encephalopath* ADJ2 bilirubin) AND CENTRAL:TARGET | 4192 |
| 12 | #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 | 4192 |
| 13 | MESH DESCRIPTOR Phototherapy EXPLODE ALL AND CENTRAL:TARGET | 3612 |
| 14 | phototherap* OR (photoradiation ADJ3 therap*) OR (light ADJ3 therap*) AND CENTRAL:TARGET | 5827 |
| 15 | #13 OR #14 | 6982 |
| 16 | #4 AND #12 AND #15 | 793 |

## Appendix 2. MEDLINE strategy

| | | |
|---|---|---|
| | Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to January 28, 2022 | |
| | Search date: January 31, 2022 | |
| # | Searches | Results |
| 1 | exp hyperbilirubinemia/ or exp hyperbilirubinemia, neonatal/ or exp jaundice, neonatal/ or exp jaundice/ or exp jaundice, obstructive/ or exp kernicterus/ | 27027 |
| 2 | (hyperbilirubinemi* or hyperbilirubinaemi* or bilirubinemi* or bilirubinaemi*).mp. | 13409 |
| 3 | (jaundice or jaundices or jaundiced).mp. | 45237 |
| 4 | kernicterus.mp. | 1840 |

*(Continued)*

| | | |
|---|---|---|
| 5 | icter*.mp. | 7776 |
| 6 | (encephalopath* adj2 bilirubin).mp. | 561 |
| 7 | or/1-6 [Jaundice] | 58576 |
| 8 | exp phototherapy/ | 48275 |
| 9 | phototherap*.mp. | 17552 |
| 10 | (photoradiation adj3 therap*).mp. | 177 |
| 11 | (light adj3 therap*).mp. | 11586 |
| 12 | or/8-11 [Phototherapy] | 55612 |
| 13 | exp infant, newborn/ or Intensive Care, Neonatal/ or Intensive Care Units, Neonatal/ | 647340 |
| 14 | (baby* or babies or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born? or newly born or premature or pre-mature or pre-matures or prematures or prematurity pre-maturity or preterm or preterms or pre term? or preemie or preemies or pre-mies or premie or VLBW or LBW or ELBW or NICU).ti,ab,kw,kf. | 953391 |
| 15 | or/13-14 [Filter: Neonatal Population 01-2022--MEDLINE] | 1236419 |
| 16 | randomized controlled trial.pt. | 557239 |
| 17 | controlled clinical trial.pt. | 94671 |
| 18 | (randomized or randomised).ti,ab. | 708913 |
| 19 | placebo.ab. | 225169 |
| 20 | drug therapy.fs. | 2435446 |
| 21 | randomly.ab. | 374953 |
| 22 | trial.ab. | 585399 |
| 23 | groups.ab. | 2304386 |
| 24 | (quasirandom* or quasi-random*).ti,ab. | 5297 |
| 25 | exp animals/ not humans/ | 4950739 |
| 26 | (or/16-24) not 25 [RCT Filter-Based on Cochrane- Box 6.4.c: Cochrane Highly Sensitive Search Strategy] | 4595292 |
| 27 | 7 and 12 and 15 [Jaundice & Phototherapy & Neonate] | 2734 |
| 28 | 26 and 27 [RCT Results Medline] | 725 |

## Appendix 3. Embase strategy

| | | |
|---|---|---|
| | Embase 1974 to 2022 January 28 | |
| | Search date: January 31, 2022 | |
| # | Searches | Results |
| 1 | exp jaundice/ or kernicterus/ or newborn jaundice/ | 58041 |
| 2 | exp hyperbilirubinemia/ | 76660 |
| 3 | (hyperbilirubinemi* or hyperbilirubinaemi* or bilirubinemi* or bilirubinaemi*).mp. | 26710 |
| 4 | (jaundice or jaundices or jaundiced).mp. | 71565 |
| 5 | kernicterus.mp. | 2391 |
| 6 | icter*.mp. | 8574 |
| 7 | or/1-6 [Jaundice] | 96138 |
| 8 | exp phototherapy/ | 100952 |
| 9 | (phototherap* or (photoradiation adj3 therap*)).mp. | 32625 |
| 10 | or/8-9 [Phototherapy] | 103884 |
| 11 | Randomized controlled trial/ or Controlled clinical study/ | 882058 |
| 12 | random$.ti,ab,kw. | 1753635 |
| 13 | Randomization/ | 92841 |
| 14 | placebo.ti,ab,kw. | 335930 |
| 15 | ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,kw. | 252672 |
| 16 | double blind procedure/ | 191703 |
| 17 | (controlled adj7 (study or design or trial)).ti,ab,kw. | 398058 |
| 18 | parallel group$1.ti,ab. | 28774 |
| 19 | (crossover or cross over).ti,ab. | 114490 |
| 20 | ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. | 371547 |
| 21 | (open adj label).ti,ab. | 94148 |
| 22 | or/11-21 [ Terms based on Cochrane Central strategy-https://www-cochranelibrary-com.ezproxy.uvm.edu/central/central-creation] | 2511851 |

(Continued)

| | | |
|---|---|---|
| 23 | (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) and (human/ or normal human/ or human cell/) | 23210414 |
| 24 | exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ | 30038201 |
| 25 | 24 not 23 [Animal Exclusion-https://community-cochrane-org.ezproxy.uvm.edu/sites/default/files/uploads/inline-files/Embase%20animal%20filter.pdf] | 6827787 |
| 26 | 22 not 25 [Filter: RCT-EMBASE] | 2243794 |
| 27 | newborn/ or prematurity/ or newborn intensive care/ or newborn care/ | 638499 |
| 28 | (baby* or babies or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born? or newly born or premature or pre-mature or pre-matures or prematures or prematurity or preterm or preterms or pre term or preemie or preemies or premies or premie or VLBW or LBW or ELBW or NICU).ti,ab,kw,kf. | 1119136 |
| 29 | or/27-28 [Filter: Neonatal Population 2021-OVID EMBASE] | 1336133 |
| 30 | 7 and 10 and 26 and 29 | 565 |

## Appendix 4. Protocol search methods

### Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Review Group as outlined in The Cochrane Library was used. The following sources were searched for eligible reports in any language:

### Electronic searches

Searches of electronic databases included:

- The Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE (1966 to the present);
- Embase(1980 to the present);
- CINAHL (1982 to the present).

The search string for searching CENTRAL and MEDLINE via PubMed included the following terms: Jaundice OR Hyperbilirubinemia OR Hyperbilirubinaemia OR Bilirubin encephalopathy OR Kernicterus OR High serum bilirubin AND Neonate OR Neonatal OR Baby OR Babies OR Child OR Infant OR Infants OR Neonates AND Phototherapy OR Phototherapeutic OR Phototherapeutics OR Light therapy OR Phototherapies.

A similar search string was used for searching Embase and CINAHL via Ovid. The search terms were adapted to the structured vocabulary, syntax, and limits required for these databases.

### Search strategies:

***MEDLINE via Ovid - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R):***

1. exp infant, newborn/
2. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or infantile or infancy or neonat*).ti,ab.
3. 1 or 2
4. (phototherap* or light therapy).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5. randomised controlled trial.pt.
6. controlled clinical trial.pt.
7. randomized.ab.
8. placebo.ab.
9. drug therapy.fs.
10. randomly.ab.
11. trial.ab.
12. groups.ab.
13. or/5-12
14. exp animals/ not humans.sh.
15. 13 not 14
16. 3 and 4 and 15

***Embase via Ovid:***

1. exp prematurity/
2. exp infant/
3. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or infantile or infancy or neonat*).ti,ab.
4. 1 or 2 or 3
5. (human not animal).mp.
6. (randomised controlled trial or controlled clinical trial or randomised or placebo or clinical trials as topic or randomly or trial or clinical trial).mp.
7. 4 and 5 and 6
8. (phototherap* or light therapy).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
9. 7 and 8

***CINAHL:***

(infant or infants or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW) AND (randomised controlled trial OR controlled clinical trial OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial) AND (phototherapy or light therapy or bright light therapy or illumination therapy)

***Searching other resources***

Abstracts presented in the past years at the annual meetings of the European Society for Paediatric Research and The Society for Pediatric Research were searched from the journal Pediatric Research and Abstracts On Line.

We searched the WHO clinical trials registry platform, and specifically the following websites:http://www.clinicaltrials.gov and http://www.controlled-trials.com for ongoing studies.

Handsearches of the reference lists of all pertinent reviews and studies found were undertaken.

Where possible, authors of identified trials were contacted to find out if they were aware of other published or unpublished trials.

## Appendix 5. Risk of bias tool

**Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?**

For each included study, we categorised the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

**Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?**

For each included study, we categorised the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);

- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

**Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?**

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

**Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?**

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

**Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?**

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk

**Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?**

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

**Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?**

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk; or
- unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

## Appendix 6. Trial registry strategies

| | |
|---|---|
| Search date: January 31, 2022 | |
| ISRCTN | |
| | |
| Text word: (bilirubin OR hyperbilirubinaemia OR hyperbilirubinemia OR jaundice) AND Interventions: Phototherapy Remove filter | 5 |
| Text word: intermittent AND Intervention: phototherapy | 0 |
| | |
| ICTRP (WHO International Clinical Trials Registry Platform) | |
| jaundice AND phototherapy AND intermittent | 4 |
| jaundice AND phototherapy | |
| hyperbilirubinemia AND phototherapy AND intermittent | 4 |
| hyperbilirubinaemia AND phototherapy AND intermittent | 0 |
| infant AND phototherapy AND intermittent | 0 |
| infants AND phototherapy AND intermittent | 2 |
| newborn AND phototherapy AND intermittent | 0 |
| newborns AND phototherapy AND intermittent | 1 |
| neonates AND phototherapy AND intermittent | 0 |
| phototherapy AND intermittent [Restricted to trials in children] | 6 |
| | |
| clinicaltrials.gov | |
| | |
| phototherapy AND intermittent AND condition: Hyperbilirubinemia | 1 |
| intermittent phototherapy AND Hyperbilirubinemia AND Child (trials in) | 1 |
| intermittent phototherapy AND Child (trials in) : found 21 but only 1 related to jaundice or hyperbilirubinemia; | 1 |
| Total | 25 |
| Duplicates (compared to trial records found by Cochrane Central searches) | 25 |
| Net | 0 |

## HISTORY

Protocol first published: Issue 4, 2009

## CONTRIBUTIONS OF AUTHORS

ABO, KGS and FW contributed to the protocol (Onyango 2009).

SB and TS co-ordinated the review.

SBG, LL and TS assessed studies for eligibility, performed critical appraisal of eligible studies and data extraction.

SBG, LL, SB, KGS and TS formed a consensus on the conclusions.

SBG and TS wrote the review with input from LL, SB and KGS.

MF wrote search strategies, reported on the results of the search and prepared the PRISMA diagram.

Guarantor for the review: TS

## DECLARATIONS OF INTEREST

SBG was involved in one of the RCTs included for final analysis (Gottimukkala 2021). It was a self-funded RCT. The study was conducted in the Departments of Neonatology & Allied Health Sciences, Chettinad Hospital & Research Institute, Chennai, India. SBG did not make study eligibility decisions about, extract data from, carry out the risk of bias assessments for, or perform GRADE assessments for this study. This study was assessed by TS and independently cross-checked by LL. SBG was not involved in determining the overall study inclusion criteria.

LL has no interest to declare.

SB has no interest to declare.

KSG is a Senior editor of Cochrane Neonatal. He was not involved in the editorial process for this review.

MF is Managing Editor and Information Specialist with the Cochrane Neonatal Group; she was not involved in the acceptance of this review.

TS has no interest to declare.

## SOURCES OF SUPPORT

### Internal sources

- Nil, Australia

  Self-funded

### External sources

- Vermont Oxford Network, USA

  Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Onyango 2009).

- Inclusion of cluster-randomised trials in Types of studies
- The inclusion criteria states, "We included infants (both term and preterm) up to the age of 30 days with jaundice or hyperbilirubinaemia requiring phototherapy." This included some studies where the initiation of phototherapy might be considered 'prophylactic' because we still considered that they were treating hyperbilirubinaemia.
- Changed the qualification of the secondary outcome "Infant mortality" from "as a result of complications of hyperbilirubinaemia" to "all cause" in Secondary outcomes
- Added an introductory paragraph in Data collection and analysis
- Addition of paragraph referring to PRISMA flow diagram in Selection of studies
- Specified reporting analyses of primary outcomes only in Sensitivity analysis

- Addition of the following sections: Unit of analysis issues; Dealing with missing data; Assessment of reporting biases; Data synthesis; Subgroup analysis and investigation of heterogeneity; Summary of findings and assessment of the certainty of the evidence
- Minor amendments made to the following sections: Assessment of heterogeneity; Subgroup analysis and investigation of heterogeneity
- We did not search CINAHL as stated in the protocol because Cochrane CENTRAL now includes records from this database.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Bilirubin; Family; *Jaundice, Neonatal; Phototherapy

### MeSH check words

Humans; Infant; Infant, Newborn