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OXIDATIVE STRESS AND INFLAMMATORY ALTERATIONS DURING PHOTOTHERAPY OF NEONATAL ICTERUS: SYSTEMATIC REVIEW AND META-ANALYSIS

Hemakshi Chaudhari[1], Chandrakant Gawli[2], Anoop Kumar,[3*] Dr. Chandragouda R. Patil.[2*]

[1]Department of Clinical Pharmacy, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dist- Dhulia, Maharashtra, India. (hemakshi_c@yahoo.com)
[2*]Department of Pharmacology, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dist- Dhulia, Maharashtra India (crpatil@rcpatelpharmacy.co.in)
[3]Department of Pharmacology and Clinical research, Delhi Pharmaceutical Sciences & Research University (DPSRU), New Delhi India (anoopniper@gmail.com)

Work Address: Karwand Naka, Shirpur, Dist- Dhule, Maharashtra (425405). Tel No :(02563) 255189 (Office) 09823400240 (Mobile), Fax :(02563) 251808.

***Corresponding Author:** Dr. Chandragouda R. Patil
Professor and HOD, Department of Pharmacology, R.C.Patel Institute of Pharmaceutical Education and Research Karwand Naka, Shirpur, Dist- Dhule, Maharashtra (425405), Tel No :(02563) 255189 (Office); 09823400240 (Mobile)Fax :(02563) 251808, crpatil@rcpatelpharmacy.co.in, pchandragouda@yahoo.com

Dr. Anoop Kumar
Assistant Professor, Department of Pharmacology and Clinical Research,Delhi Pharmaceutical Sciences & Research University (DPSRU), New Delhi, Delhi 110017, **Phone:** 011 2955 2039, Email: anoopniper@gmail.com

Abstract

Purpose: Phototherapy is used in the treatment of neonatal hyperbilirubinemia. There are contravening reports on its its adverse effect. This meta-analysis was conducted to substantiate the impact of phototherapy on the parameters indicating oxidative stress and pro-inflammatory cytokines.
Methods: The relevant clinical studies were searched on PubMed, Google Scholar, Stanford University High-Wire Press, Clinical trial registry, and on Semantic Scholar published up to 30th July 2022. Newcastle-Ottawa Scale was used to assess the study qualities. The overall estimate was calculated in terms of odds ratio with 95% confidence interval using random effect model. The sensitivity and subgroup analysis were carried out along with the qualitative assessment of the publication bias. All the analysis was carried out using RevMan 5.
Results: Total 1735 participants from 31 pertinent studies were used for the quantitative analysis. The pooled estimates of the phototherapy-exposed group were compared with the control group. Our analysis revealed that phototherapy used in treating neonatal jaundice induced significant oxidative stress and increased the levels of inflammatory cytokines. Overall estimate measure i.e., mean difference was found to be significant [1.39 (0.79 1.99)] for MDA (nmol per ml), [-0.87 (-1.35 -0.39)] for MDA (nmol per litre) [-0.25 (-0.34 -0.15)] for TAC, [-81.68 (-105.50 -57.85)] for TNF-α, and non-significant for TOS and IL-6 i.e [1.36(-2.67 5.39)] and [1.96 (-0.89 4.81)] respectively

Conclusion: Therapeutic exposure to phototherapy in treating neonatal jaundice induces a rise in oxidative stress and inflammatory cytokine levels. The short and long-term clinical outcomes may have clinical significance.

Keywords: Neonatal Jaundice, Oxidative Stress, Malondialdehyde, Total Antioxidant Capacity, Total Oxidative Stress, Cytokines, TNF-α, IL-6

Introduction

Neonatal jaundice (NJ) is a common condition associated with hyperbilirubinemia occurring in about 50% of full term and almost 80% of preterm new-borns (1-3). It may subside without treatment within three weeks after birth and most of the infants with the NJ may not require active treatment. However, in severe cases, the hyperbilirubinemia and consequent encephalopathy may even prove fatal particularly in the cases of intravascular haemolysis (1). Apart from the use of enzyme-induction therapy, the mainstay treatment of NJ involves exposure of the affected new-born to phototherapy (PT). Due to the presence of endogenous photosensitizers generating singlet oxygen and other reactive oxygen species (ROS) the phototherapy may induce oxidative stress and inflammatory cytokines(2). The ROS may induce oxidation of biological macromolecules and damage the lipid membrane, alter enzyme functions, damage DNA (Deoxyribonucleic acid), and ultimately induce cell death (3, 4). In phototherapy, either natural light or artificial light with 460 nm wavelength is used. But the use of natural light is not a therapy, at least in Europe and many other countries. At this wavelength, the light maximally penetrates the skin/tissues and induces photoisomerization of the bilirubin rendering it more soluble and hence easily excretable (5,6,7). The intensity and wavelength of the light used in phototherapy have a significant impact on the rate of bilirubin isomerization (5).

In the new-borns, the red blood cells (RBCs) are highly vulnerable to oxidative damages. Exposure to phototherapy may precipitate adverse effects in the vulnerable new-borns with low birthweight (6), in preterm infants (7), and in those suffering from congenital diseases (8). Such infants have a weaker innate antioxidative capacity as compared to their normal counterparts (9).

The side effects of phototherapy are customarily considered not severe and adequately manageable. However, recent research has revealed that the exposure to therapeutic phototherapy induces unforeseeable untoward effects in the vulnerable neonates. The retrospective studies indicating long term consequences of phototherapy are cautioning about its restricted use only in the healthy new-borns (9, 10). Thus, choice of phototherapy in treating NJ becomes a quick decision that calls for a collection of reliable data and comparative research on the unfavourable effects of phototherapy and on the factors affecting its untoward effects (12).

This meta-analysis is an effort to corroborate the role of phototherapy on the oxidative stress and on inflammatory cytokine levels in the infants with hyperbilirubinemia.

Methodology

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) standards were followed for this study. The protocol is registered with International Prospective Register of Systematic Reviews (PROSPERO), with the accession number **[CRD42022330749].**

Search strategy

The relevant literature was searched using PubMed, Google Scholar, Stanford University Highwire Press, Clinical trial registry, and Semantic Scholar up to 30th July 2022 using designed MeSH terms. The MeSH terms with Boolean operators that were used to search the literature were as follows: ((((Neonatal jaundice) OR (Neonatal icterus)) OR (Neonatal hyperbilirubinemia)) OR (New born jaundice) OR (New born icterus) OR (New born hyperbilirubinemia) OR (Infant jaundice) OR (New born icterus) OR (New born hyperbilirubinemia)) AND (Phototherapy)) OR (Blue light)) OR (LED)) OR (Conventional phototherapy)) OR (Fibre optic))) AND (Malondialdehyde)) OR (Total Antioxidant Capacity)) OR (Total Oxidative Stress)) OR (GSH) OR (Catalase)) OR (Oxidative

Stress)) OR (Antioxidant Status) AND (Cytokines)) OR (Tumour necrosis factor alpha)) OR (Interleukins))) OR (Interleukin-6)) OR (TNF-α))

Study selection

The studies included were a) confirmed hyperbilirubinemia cases exposed to phototherapy, b) all or at least one oxidative stress parameter Malondialdehyde (MDA), Total Antioxidant Capacity (TAC), Total Oxidative Stress (TOS), Tumor Necrosis Factor Alpha (TNF-α,) Interleukin-6 (IL-6) being estimated before and after the exposure to phototherapy, c) preterm, term and full-term babies, d) both male and female participants and, e) studies with results given as mean and standard deviation.

The excluded studies were those with the following characteristics- a.) Studies in which new-borns were not exposed to phototherapy b.) case reports, animal studies, case series, narrative review, systematic review, meta-analysis

Two authors (HEC and CG) separately screened all the articles to check their compliance with the inclusion criteria. The full text articles were screened individually by the two authors (HEC and CG) and in case of any conflicts over the inclusion, the third and fourth authors (CRP and AK) were consulted.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of studies. Two reviewers (HEC and CG) independently completed the evaluation. The studies were classified into three groups, based on their quality: good, fair, and poor as given in **Table 1 (Table 1 Quality assessment using Newcastle Ottawa scale.)**

Data extraction

The study details retrieved in the literature including publication year, location of the study (country), study design, number of new-borns exposed to phototherapy, type of phototherapy used, wavelength, intensity and duration of exposure, and the distance of the light source from the baby were extracted from full-text articles and entered into an excel spreadsheet by two authors (HEC and CG) as revealed in **Table 2**.

(**Table 2 Study characteristics of Included studies)**

Sensitivity analysis

The data analyses were performed using RevMan 5. Overall estimate was calculated as odds ratio with 95% confidence intervals using a random effect model. We used random effect model considering the heterogeneity among the studies. Cochrane Q and I^2 statistics was used to calculate variability among studies. Funnel plot was used to estimate publication bias. The effect of high and low levels of parameters on the study outcomes was checked by performing the sensitivity analysis. Funnel Plots are provided in supplementary file.

Results

Search results and study characteristics

Initially we retrieved 113 relevant articles using different databases. We eliminated total 30 duplicate articles and 8 articles that were the most irrelevant. HEC and CG screened 75 articles by going through all the abstracts separately. Considering the exclusion criteria, total 30 records were excluded after screening and ultimately 46 full text articles were downloaded. Out of these, 14 articles were found to contain insufficient analysable data (unit differences and missing SD values) and hence these were excluded. Finally, 33 articles were screened. Two studies were further excluded as these studies have mentioned MDA/TAC as prooxidant/antioxidant balance which was unique for these all studies and hence we could not be included it in the analysis. Finally, 31 studies were included. Among these 31 studies, 28 were observational studies and 03 were controlled trials. Initially analysis was done for all these 31 studies. and a separate analysis of observational studies was also done in subgroup analysis.

All the excluded and included data along with the justifications are provided in supplementary file of this study.

Finally following 31 articles were found to be appropriate for quantitative analysis which are presented in **Fig.1**. (**Fig. 1. Selection of studies as per the PRISMA Checklist)**

Abdellatif *et al.,* 2012(13) Akisu, 1998;(14) Allam *et al.,* 2017;(15) Askaray, 2018;(16) Awad, 2020;(17) Aycicek, 2007;(4) Ayyapan *et al.,* 2015; (18)Bulut, 2019;(19) Dogan *et al.,* 2011; (20) Demirel *et al.,* 2010;(11) Demirtas, 2022; (21) Erdam *et al.,* 2011; (22) EI-Farrash *et al.,* 2018; (23)Gathwala, 2002; (24)Kaplan, *et al.,* 2005;(3) Kurban et al., 2014; (22)Kurt *et al.,* 2009; (25)Midam *et al.,* 2022; (26)Mustafa *et al.,* 2021; (27)Naem, 2020;(28) Ozutre, 2000;(29) Putra, 2018;(30) Saber *et al.,* 2014;(31) Shahaswari *et al.,* 2017; (32)Sheikh et al., 2022, (33)Sidrah *et al.,* 2015;(34) Sirota *et al.,* 1999;(35) Sarici *et al.,* 2015;(36) Thaigarjan, 2010; (37)Tekgundiz *et al.,* 2016; (38)Zarkesh *et al.,* 2016(39)

Among 31 studies, 12 studies were conducted in Turkey, 09 studies in Egypt, 05 studies in India, 02 studies in Israel, and a single study each in Iran and Indonesia. location of Ozutre 2000 could not be obtained, as it was communicated as letter to editor. Among these included studies, 28 studies were observational studies (pre-test and post-test) and 3 studies were randomized controlled trials (RCTs).

Quality assessment

The NOS for quality assessment categorised 08 of the 31 studies as good quality, 13 as fair quality, and the remaining 10 as poor quality studies **(Table 1)**.

The good quality studies Awad, 2020; Allam *et al.,* 2017; Demirel *et al.,* 2010; EI-Farrash *et al.,* 2018; Kaplan *et al.,* 2005; Kurt *et al.,* 2009; Putra, 2018; Sarici *et al.*, 2015; and Sirota *et al.,* 1999; provided detailed specifications of the phototherapy device, light sources used, duration of exposure, distance of the baby from light source, irradiance and wavelength of the light. In the other studies like Akisu, 1998; Askaray, 2018; Aycicek,2007; Erdam *et al.,* 2011; Gathwala, 2002; Kurt *et al.,* 2009; Mustafa *et al.,* 2021; Thaigarjan, 2010 either wavelength or irradiance of the light was missing while in the studies by Bulut, 2019; Kurban *et al.,* 2014; Shahaswari *et al.,* 2017; Kurban *et al.,* 2014; and Tekgundiz *et al.,* 2016 either the type of light source or the distance of the baby from light source was missing. In the study by Zarkesh *et al*., 2016, the type of phototherapy device and irradiance intensity of light was missing. Studies with a poor quality, Abdellatif *et al.,* 2012; Ayyapan *et al.,* 2015; Demirtas, 2022; Dogan *et al.,* 2011; Midan *et al.,* 2022; Naem, 2020; Ozutre, 2000; Saber *et al.,* 2014; Sidrah et al., 2015; and Sheikh *et al.,* 2022, the specification of the device were mentioned however, the duration of exposure was missing.

It was observed in the selected studies that either white or blue fluorescent light were used for phototherapy except in the study described by Allam *et al.,* 2017**;** Demirel *et al.,* 2010; and EI-Farrash *et al.,* 2018 where author has compared the effects of Light Emitting Diode (LED)and fluorescent light. The duration of exposure was 24, 48 and 72 hours in most of the studies. In only four of the studies Abdellatifs *et al.,* 2012; Demirel *et al.,* 2010; Demirtus, 2022; Gathwala 2002; Midan *et al,* 2022; and Mustafa., 2021, the duration of exposure was 12, 32-36, 12, 96, 98.3-114.5 and 1-2 hours respectively. Distance of the baby from the light source was 30-40 cm in all the studies except in Putra, 2018, where it was 20 cm. The intensity of irradiance of the light was between 8-20 μW/cm2/nm in all the studies except in the studies by Sarici 2015 (35 μW/cm2/nm) and Allam 2017 (8-12 μW/cm2) for conventional fluorescent device and 30-40 μW/cm2/nm for LED device. Wavelength of light used for phototherapy was between 400-500 nm in all the studies.

Use of phototherapy in neonatal hyperbilirubinemia patients

This meta-analysis includes a total 1735 new-borns treated with phototherapy for hyperbilirubinemia. The study parameters included oxidative stress parameters (MDA, TAC, TOS) and inflammatory cytokines (TNF-α, IL-6) estimated before and after the exposure to phototherapy. The overall estimates were [1.39 (0.79 1.99)] for MDA (nmol per ml) **Fig.2 [Fig. 2. Pooled analysis results using**

a random effect model (Forest plot): Malondialdehyde (nmol per ml)], [-0.87 (-1.35 -0.39)] for MDA (nmol per litre) **Fig.3** [Fig. 3. **Pooled analysis results using a random effect model (Forest plot): Malondialdehyde (nmol per liter)]** [-0.25 (-0.34 -0.15)] for TAC **Fig 4 [Fig. 4. Pooled analysis results using a random effect model (Forest plot): Total Antioxidant Capacity (mmol Trolx/L)],** [-81.68 (-105.50 -57.85)] for TNF-α **Fig. 5. Pooled analysis results using a random effect model (Forest plot): TNF alpha**, and non-significant for TOS and IL-6 i.e [1.36(-2.67 5.39)] **Fig. 6 (Fig.6. Pooled analysis results using a random effect model (Forest plot): Total Oxidative Stress**] and [1.96 (-0.89 4.81)] **Fig 7 [Fig.6. Pooled analysis results of alpha using a random effect model (Forest plot): IL-6]**. These outcomes indicate a significant perturbation in oxidative stress and a rise in the pro-inflammatory cytokines in the phototherapy exposed new-borns as compared to the control group. The asymmetry observed in the funnel plot may be attributed to the variability among the studies.

Sensitivity analysis

The sensitivity analysis was carried out to examine how very high and very low levels of proinflammatory cytokines and ROS parameters affect the results. In total 19 studies, MDA was measured before and after the exposure to phototherapy, however even amongst these studies, in only 4 it was measured in nmol per litre while in 13 studies it was in nmol per ml. Hence, a separate analysis was performed for these studies considering the difference in the units of the parameter.

In case of studies where MDA was estimated in nmol per ml, the studies by **Acyicek, 2007; Ozutre, 2000 and Sidrah *et al.,* 2005** reported a very low levels of MDA whereas three studies **i.e., EI-Farrash *et al.,* 2018**; **Kaplan *et al.,* 2005; Putra, 2018; Thaigarjan *et al.,* 2010** reported higher levels of MDA. Pooled OR was found to be [-1.21 (-0.84 0.42)] **Fig. 8. [Pooled analysis results using a random effect model (forest plot): Malondialdehyde (nmol per ml) Excluding High and Low levels]** after exclusion of the studies with high as well as low values.

In the study, where MDA was estimated in nmol per litre i.e., Akisu 1998 in preterm and full term new-borns a very high levels of MDA was reported in the new-borns both before and after exposure and the pooled OR was found to be [0.85 (-1.36 0.34)] **Fig. 9. [Fig. 9. Pooled analysis results using a random effect model (forest plot): Malondialdehyde (nmol per liter)]** after removal of these outliers

In case of studies where TOS was estimated, the studies by **Bulut, 2019, Dogan *et al.,* 2011, Kurban *et al.,* 2014, Demirel *et al.,* 2010 and Demirtus, 2022** found very high values of TOS before and after exposure to phototherapy**.** Pooled OR was found to be [1.42 (-1.95 4.80)] **Fig. 10 [Fig. 10. Pooled analysis results using a random effect model (forest plot)]: Total Oxidative Stress** after exclusion of these outliers. The conclusion of initial analysis was not affected after the removal of these studies with a low and high levels of TOS**.**

The exclusion of all the extreme values of parameters did not affect the conclusion of the study.

Table 1 Quality assessment using Newcastle Ottawa scale.

Sr. No	Author and Year	Selection	Comparability	Exposure	Total Score	Quality
1	Abdellatif et al., 2012	*	**	***	06	Poor
2	Akisu, 1998	**	**	***	07	Fair
3	Allam et al., 2017	***	**	***	08	Good
4	Askaray, 2018	**	**	***	07	Fair
5	Awad, 2020	***	**	***	08	Good
6	Aycicek 2007	**	**	***	07	Fair
7	Ayyapan et al., 2015	*	**	***	06	Poor
8	Bulut, 2019	**	**	***	07	Fair
9	Demirel et al., 2010	***	**	***	08	Good
10	Demirtus, 2022	*	**	***	06	Poor

11	**Dogan et al., 2011**	*	**	***	**06**	**Poor**
12	**Erdam et al., 2011**	**	**	***	**07**	**Fair**
13	**EI- Farrash et al., 2018**	***	**	***	**08**	**Good**
14	**Gathwala 2002**	**	**	***	**07**	**Fair**
15	**Kaplan, et al., 2005**	***	**	***	**08**	**Good**
16	**Kurban et al., 2014**	**	**	***	**07**	**Fair**
17	**Kurt et al., 2009**	***	**	***	**08**	**Good**
18	**Midan et al, 2022**	*	**	***	**06**	**Poor**
19	**Mustafa et al 2021**	**	**	***	**07**	**Fair**
20	**Naem, 2020**	*	**	***	**06**	**Poor**
21	**Ozutre, 2000**	*	**	***	**06**	**Poor**
22	**Putra, 2018**	***	**	***	**08**	**Good**
23	**Saber et al., 2014**	*	**	***	**06**	**Poor**
24	**Shahaswari et al., 2017**	**	**	***	**07**	**Fair**
25	**Sheikh et al., 2022**	*	**	***	**06**	**Poor**
26	**Sidrah et al., 2015**	*	**	***	**06**	**Poor**
27	**Sarici et al., 2015**	***	**	***	**08**	**Good**
28	**Sirota et al 1999**	***	**	***	**08**	**Good**
29	**Thaigarjan, 2010**	**	**	***	**07**	**Fair**
30	**Tekgundiz et al., 2016**	**	**	***	**07**	**Fair**

Heterogeneity

The I^2 (more than 90) and the chi^2 values indicated very high heterogeneity among the studies. However, removal of the outliers only slightly changed the I^2 values

Sub-group analysis

The sub-group analysis was carried out to examine the difference of trends in all the observational studies except the randomized controlled trial. For the studies related with MDA (nmol per ml), the pooled OR was found to be 0.20 [-0.33 0.73], **Fig.11[. Pooled analysis results of observational studies using a random effect model (forest plot): Malondialdehyde (nmol per ml)** For the studies related to TAC, the OR was **[-0.27 (-0.38 - 0.15)] Fig. 12 [Fig. 12. Pooled analysis results of observational studies using a random effect model (forest plot): Total Antioxidant Capacity]** and for the studies of TOS, the pooled OR was found to **[1.45 (-1.76 4.66]** Fig.13. **[Pooled analysis results using a random effect model (forest plot): Total Oxidative Stress]**

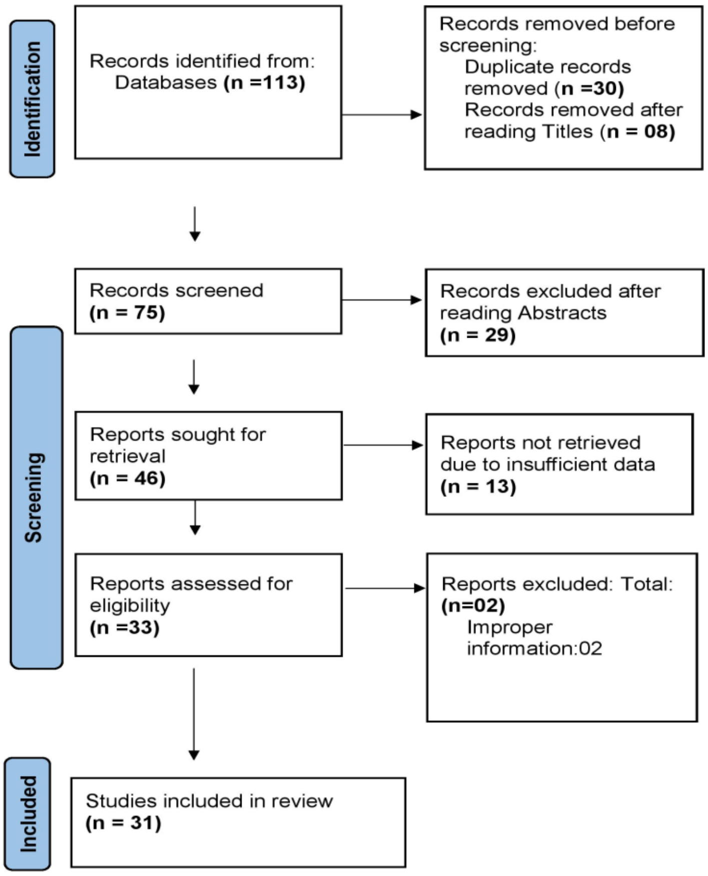
Table 2 Study characteristics of Included studies

Sr. No	**Author and Year**	**Study Design**	**Location**	**Age**	**Category**	**Sample Size**	**Type of Light**	**Duration of PT**	**Distance in cm**	**Parameter**	**Irradiance**
1	Abdellatif et al., 2012	Observational	Egypt	1--8	Full term	50	NM	12	NM	MDA	NM
2	Akisu, 1998	Observational	Turkey	8--10	Preterm Full term	36	White fluorescent	72	40	MDA	11
3	Allam et al., 2017	Observational	India	1--7	Preterm	82	Fluorescent light /LED	48	30-40 cm	TAC, TOS	8--12, 30--40

4	Askaray, 2018	Observational	Egypt	3--4	Full term	90	Five Blue Lights	72	30 cm	TNF alpha, IL-6	NM
5	Awad, 2020	Observational	Egypt	3--7	Late Preterm	15	4 Blue fluorescent	48	25-30	TAC, TOS	20--26
6	Aycicek 2007	Observational	Turkey.	3--10	Full term	57	Six white fluorescents	48	40	MDA, TAC, TOS	12--16
7	Ayyapan et al., 2015	Observational	India	2--15	NM	50	NM	NM	50	MDA	NM
8	Bulut, 2019	Observational	Turkey	2--8	Full term	68	NM	24	NM	TAC,TOS	12--16
9	Demirel et al., 2010	RCT	Turkey	1--7	Late Preterm		six fluorescent lamps and LED phototherapy	32-36	30	TAC, TOS	Conventional:12-16 µW/cm2/nm and LED:30 µW/cm2/nm
10	Demirtus, 2022	RCT	Turkey	1--7	Term	60	LED	12	NM	TAC, TOS	NM
11	Dogan et al., 2011	Observational	Turkey	2--10	Full term	69	NM	NM	NM	MDA, TAC, TOS	NM
12	Erdam et al., 2011	Observational	Turkey	3--13	Full term	30	16 White Fluroscent	NM	40	MDA	20-26
13	EI-Farrash et al., 2018	RCT	Egypt	1--15	Term	120	Fluroscent, LED, Intensive	24	35	MDA	Fluroscent-12-16, intensive-more than 60, LED-30-120
14	Gathwala 2002	Observational	India	1--8	Preterm	30	Blue fluorescent	96	30	MDA	11
15	Kaplan, et al., 2005	Observational	Isralel	7--8	Preterm	41	Halogen	24	43	MDA	18
16	Kurban et al., 2014	Observational	Turkey	3--15	Full term	40	16 White fluorescent	48	40cm	TAC, TOS	NM
17	Kurt et al., 2009	Observational	Turkey	5--6	Term	37	Two white and two blue	72	30 cm	TNF alpha, IL-6	10--15

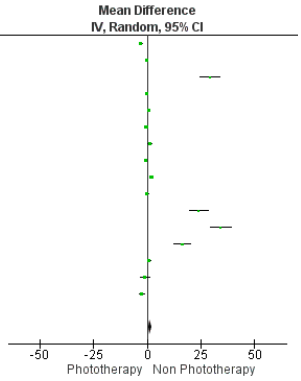
18	Midan et al, 2022	Observational	Egypt	2--4	full-term	Gp1: 12 Gp2: 40	NM	98.3-114.5	NM	MDA	NM
19	Mustafa et al 2021	Observational	Turkey	2--4	Full term	40	4 White 4 Blue	1.51	40	TAC, TOS	12--20
20	Naem, 2020	Observational	Egypt	1--7	Full term	35	NM	72	NM	TNF alpha,	NM
21	Ozutre, 2000	Observational	NM	NM	NM	NM	NM	NM	NM	MDA	NM
22	Putra, 2018	Observational	Indonesiia	2--14	Full term	30	Blue fluorescent	24	20	MDA	10
23	Saber et al., 2014	Observational	Egypt	4	Term	30	NM	72	30 cm	TNF alpha	NM
24	Shahaswari et al., 2017	Observational	Iran	6--10	late preterm	35	MicroLite	48	NM	MDA	13
25	Sheikh et al., 2022	Observational	Egypt	1--15	Full term	100	NM	72	NM	TNF alpha	18--12
26	Sidrah et al., 2015	Observational	India	1--10	Preterm full term	60	NM	NM	NM	MDA	NM
27	Sarici et al., 2015	Observational	Turkey	5--7	term, full term	62	Gallium Nitride	24	40	MDA	35
28	Sirota et al 1999	Observational	Israel	1--8	Term	50	Four white Fluorescent	24	30 cm	TNF alpha, IL-6	9
29	Thaigarjan, 2010	Observational	India	2--7	Full term	40	blue fluorescence	48	40	MDA	NM
30	Tekgundiz et al., 2016	Observational	Turkey	3--5	Preterm term	56	NM	24	NM	MDA	13
31	Zarkesh et al., 2016	Observational	Egypt	1--7	Term	90	NM	48	30 cm	TNF alpha, IL-6	NM

Fig. 1. Selection of studies as per the PRISMA Checklist.



Study or Subgroup	Phototherapy Mean	Phototherapy SD	Phototherapy Total	Non Phototherapy Mean	Non Phototherapy SD	Non Phototherapy Total	Weight	Mean Difference IV, Random, 95% CI	Random sequence generation (selection bias)
Midan et al., 2022-b	5.1	1.25	40	8.2	1.8	40	8.0%	-3.10 [-3.78, -2.42]	Unclear risk
Ozutre, 2000	0.85	0.2	19	0.99	0.15	19	8.9%	-0.14 [-0.25, -0.03]	Unclear risk
Putra, 2018	53.05	10.18	30	23.73	8.2	30	1.4%	29.32 [24.64, 34.00]	Unclear risk
Sarici et al., 2015	7.52	0.79	62	7.72	0.75	62	8.8%	-0.20 [-0.47, 0.07]	Unclear risk
Shahaswari et al., 2017	3.76	0.23	35	2.8	0.18	35	8.9%	0.96 [0.86, 1.06]	Unclear risk
Sidrah et al., 2015	2.8	0.2	60	3.227	0.227	60	8.9%	-0.43 [-0.50, -0.35]	Unclear risk
Thaigarjan, 2010	13.79	2.85	40	12.61	2.32	40	6.7%	1.18 [0.04, 2.32]	Unclear risk
Aycicek, 2007	1.98	0.33	49	2.46	0.36	57	8.9%	-0.48 [-0.61, -0.35]	Unclear risk
Ayyapan et al., 2015	7.72	0.89	50	5.72	0.62	50	8.7%	2.00 [1.70, 2.30]	Unclear risk
Dogan et al., 2011	3.47	2.15	69	3.46	1.6	69	8.1%	0.01 [-0.62, 0.64]	Unclear risk
El-Farrash et al., 2018-a	37.7	13.75	40	13.67	3.86	40	1.5%	24.03 [19.60, 28.46]	Unclear risk
El-Farrash et al., 2018-b	50.9	13.89	40	16.67	6.65	40	1.3%	34.23 [29.46, 39.00]	Unclear risk
El-Farrash et al., 2018-c	30.37	12.16	40	13.93	3.82	40	1.8%	16.44 [12.49, 20.39]	Unclear risk
Erdam et al., 2011	9.4	1.5	36	8.4	1.8	36	7.8%	1.00 [0.23, 1.77]	Unclear risk
Kaplan, et al., 2005	18.08	4.5	41	19.08	5.6	41	4.0%	-1.00 [-3.20, 1.20]	Unclear risk
Midan et al., 2022-a	5.25	1.35	12	7.8	1.87	12	6.3%	-2.55 [-3.85, -1.25]	Unclear risk
Total (95% CI)			**663**			**671**	**100.0%**	**1.39 [0.79, 1.99]**	

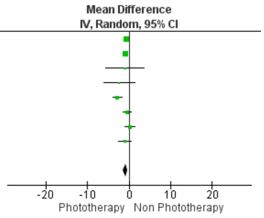
Heterogeneity: $Tau^2 = 1.05$; $Chi^2 = 1360.71$, df = 15 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 4.54$ ($P < 0.00001$)



[Fig. 2. Pooled analysis results using a random effect model (Forest plot): Malondialdehyde (nmol per ml)]

Study or Subgroup	Phototherapy Mean	SD	Total	Non Phototherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Random sequence generation (selection bias)
Abdellatif et al., 2012-a	2.44	0.6	25	3.07	0.52	25	27.2%	-0.63 [-0.94, -0.32]	Unclear risk
Abdellatif et al., 2012-b	2.59	0.47	25	3.37	0.64	25	27.2%	-0.78 [-1.09, -0.47]	Unclear risk
Akisu, 1998-a	16.31	5.4	16	17.24	7.7	16	1.1%	-0.93 [-5.54, 3.68]	Unclear risk
Akisu, 1998-b	20.116	5.9	20	22.46	6.3	20	1.5%	-2.34 [-6.13, 1.44]	Unclear risk
Gathwala, 2002	8.6	0.8	30	11.4	2.9	30	12.1%	-2.80 [-3.88, -1.72]	Unclear risk
Tekgundiz et al., 2016-a	9.9	1.48	56	10.35	3.39	56	13.7%	-0.45 [-1.42, 0.52]	Unclear risk
Tekgundiz et al., 2016-b	3.76	2.94	56	3.5	3.75	56	10.1%	0.26 [-0.99, 1.51]	Unclear risk
Tekgundiz et al., 2016-c	5.1	3.7	56	6.03	4.76	56	7.2%	-0.93 [-2.51, 0.65]	Unclear risk
Total (95% CI)			**284**			**284**	**100.0%**	**-0.87 [-1.35, -0.39]**	

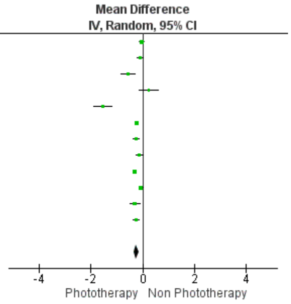
Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 18.16$, df = 7 (P = 0.01); $I^2 = 61\%$
Test for overall effect: Z = 3.54 (P = 0.0004)



[Fig. 3. Pooled analysis results using a random effect model (Forest plot): Malondialdehyde (nmol per liter)]

Study or Subgroup	Phototherapy Mean	SD	Total	Non Phototherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Random sequence generation (selection bias)
Demirel et al., 2010-a	1.9	0.2	30	1.94	0.2	30	9.7%	-0.04 [-0.14, 0.06]	Unclear risk
Demirel et al., 2010-b	1.96	0.2	30	2.05	0.29	30	9.2%	-0.09 [-0.22, 0.04]	Unclear risk
Demirtas, 2022	1.75	0.38	30	2.31	0.7	30	5.7%	-0.56 [-0.85, -0.27]	Unclear risk
Dogan et al., 2011	1.99	0.95	36	1.75	0.57	36	4.4%	0.24 [-0.12, 0.60]	Unclear risk
Kurban et al., 2014	4.26	0.57	40	5.8	0.95	40	4.6%	-1.54 [-1.88, -1.20]	Unclear risk
Mustafa et al., 2021	0.86	0.13	47	1.08	0.1	47	10.6%	-0.22 [-0.27, -0.17]	Unclear risk
Allam et al., 2017-a	0.28	0.16	41	0.53	0.36	41	9.3%	-0.25 [-0.37, -0.13]	Unclear risk
Allam et al., 2017-b	0.53	0.27	41	0.65	0.37	41	8.9%	-0.12 [-0.26, 0.02]	Unclear risk
Awad, 2020	0.48	0.02	30	0.77	0.134	30	10.6%	-0.29 [-0.34, -0.24]	Unclear risk
Aycicek, 2007	1.48	0.13	57	1.54	0.31	57	10.0%	-0.06 [-0.15, 0.03]	Unclear risk
Bulut, 2019-a	2.04	0.37	20	2.34	0.21	20	7.8%	-0.30 [-0.49, -0.11]	Unclear risk
Bulut, 2019-b	2.08	0.22	20	2.33	0.18	20	9.2%	-0.25 [-0.37, -0.13]	Unclear risk
Total (95% CI)			**422**			**422**	**100.0%**	**-0.25 [-0.34, -0.15]**	

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 108.69$, df = 11 (P < 0.00001); $I^2 = 90\%$
Test for overall effect: Z = 4.91 (P < 0.00001)



[Fig. 4. Pooled analysis results using a random effect model (Forest plot): Total Antioxidant Capacity (mmol Trolx/L)]

Study or Subgroup	Phototherapy Mean	SD	Total	Non Phototherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Random sequence generation (selection bias)
Allam et al., 2017-a	15.6	10.9	41	10.9	8.3	41	10.9%	4.70 [0.51, 8.89]	Unclear risk
Allam et al., 2017-b	14.6	10.2	41	11.8	7.9	41	11.0%	2.80 [-1.15, 6.75]	Unclear risk
Awad, 2020	16.2	3.3	30	11.92	3.297	30	12.1%	4.28 [2.61, 5.95]	Unclear risk
Aycicek, 2007	16.34	7.4	49	11.34	5.9	57	11.7%	5.00 [2.42, 7.58]	Unclear risk
Bulut, 2019-a	38.84	28.25	20	40.63	15.44	20	4.9%	-1.79 [-15.90, 12.32]	Unclear risk
Bulut, 2019-b	59.26	48.64	20	49.3	22.71	20	2.4%	9.96 [-13.57, 33.49]	Unclear risk
Demirel et al., 2010-a	51.69	25.7	30	22.78	17.8	30	6.3%	28.91 [17.72, 40.10]	Unclear risk
Demirel et al., 2010-b	26.55	14.3	30	26	16.7	30	8.4%	0.55 [-7.32, 8.42]	Unclear risk
Demirtas, 2022	28.12	9.99	30	43.86	12.35	30	9.9%	-15.74 [-21.42, -10.06]	Unclear risk
Dogan et al., 2011	10.85	6.4	36	11.1	3.84	36	11.8%	-0.25 [-2.69, 2.19]	Unclear risk
Mustafa et al., 2021	15.78	6.7	47	25.11	14.05	47	10.7%	-9.33 [-13.78, -4.88]	Unclear risk
Total (95% CI)			**374**			**382**	**100.0%**	**1.36 [-2.67, 5.39]**	

Heterogeneity: $Tau^2 = 34.39$; $Chi^2 = 102.68$, df = 10 (P < 0.00001); $I^2 = 90\%$
Test for overall effect: Z = 0.66 (P = 0.51)

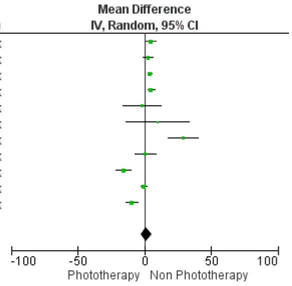
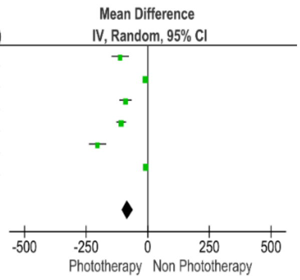


Fig. 5. Pooled analysis results using a random effect model (Forest plot): TNF alpha

Study or Subgroup	Phototherapy Mean	SD	Total	Non Phototherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Random sequence generation (selection bias)
El-Sheikh 2022	56.91	37.05	100	168.85	163.25	100	14.1%	-111.94 [-144.75, -79.13]	Unclear risk
Kurt 2009	4.47	2.37	21	15.47	9.89	21	19.1%	-11.00 [-15.35, -6.65]	Unclear risk
Naem 2020	61.36	31.96	35	151.49	61.97	35	16.3%	-90.13 [-113.23, -67.03]	Unclear risk
Saber 2014	38	25	30	146	44	30	17.3%	-108.00 [-126.11, -89.89]	Unclear risk
Sirota 1999	384	75	50	588	91	50	14.1%	-204.00 [-236.69, -171.31]	Unclear risk
Askaray 2018	8.63	4.6	90	17.6	3.2	90	19.2%	-8.97 [-10.13, -7.81]	Unclear risk
Total (95% CI)			326			326	100.0%	-81.68 [-105.50, -57.85]	

Heterogeneity: $Tau^2 = 769.78$; $Chi^2 = 334.38$, df = 5 (P < 0.00001); $I^2 = 99\%$
Test for overall effect: Z = 6.72 (P < 0.00001)



(Fig.6. Pooled analysis results using a random effect model (Forest plot)): Total Oxidative Stress]

Study or Subgroup	Phototherapy Mean	SD	Total	Non Phototherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Random sequence generation (selection bias)
Askaray 2018	38.7	19.3	90	34.6	16.8	90	17.0%	4.10 [-1.19, 9.39]	Unclear risk
Kurt 2009	10.16	20.69	21	9.71	2.7	21	8.1%	0.45 [-8.47, 9.37]	Unclear risk
Sirota 1999	24	3.9	20	20.4	2.2	20	34.2%	3.60 [1.64, 5.56]	Unclear risk
Zarkesh	1.41	0.98	97	1.42	1.17	97	40.7%	-0.01 [-0.31, 0.29]	Unclear risk
Total (95% CI)			**228**			**228**	**100.0%**	**1.96 [-0.89, 4.81]**	

Heterogeneity: $Tau^2 = 5.16$; $Chi^2 = 14.92$, df = 3 (P = 0.002); $I^2 = 80\%$
Test for overall effect: Z = 1.35 (P = 0.18)

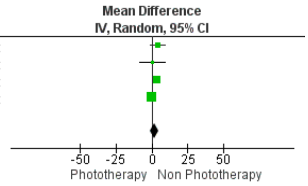


Fig 7 [Fig.7. Pooled analysis results of alpha using a random effect model (Forest plot): IL-6]

Study or Subgroup	Phototherapy Mean	SD	Total	Non Phototherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Random sequence generation (selection bias)
Aycicek, 2007	1.98	0.33	49	2.46	0.36	57	12.1%	-0.48 [-0.61, -0.35]	Unclear risk
Ayyapan et al., 2015	7.72	0.89	50	5.72	0.62	50	11.8%	2.00 [1.70, 2.30]	Unclear risk
Dogan et al., 2011	3.47	2.15	69	3.46	1.6	69	10.9%	0.01 [-0.62, 0.64]	Unclear risk
Erdam et al., 2011	9.4	1.5	36	8.4	1.8	36	10.3%	1.00 [0.23, 1.77]	Unclear risk
Midan et al., 2022-a	5.25	1.35	12	7.8	1.87	12	8.0%	-2.55 [-3.85, -1.25]	Unclear risk
Midan et al., 2022-b	5.1	1.25	40	8.2	1.8	40	10.7%	-3.10 [-3.78, -2.42]	Unclear risk
Sarici et al., 2015	7.52	0.79	62	7.72	0.75	62	11.9%	-0.20 [-0.47, 0.07]	Unclear risk
Shahaswari et al., 2017	3.76	0.23	35	2.8	0.18	35	12.1%	0.96 [0.86, 1.06]	Unclear risk
Sidrah et al., 2015	2.8	0.2	60	3.227	0.227	60	12.1%	-0.43 [-0.50, -0.35]	Unclear risk
Total (95% CI)			**413**			**421**	**100.0%**	**-0.21 [-0.84, 0.42]**	

Heterogeneity: Tau² = 0.86; Chi² = 819.97, df = 8 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.65 (P = 0.51)

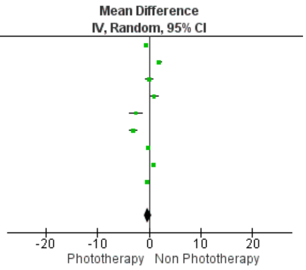
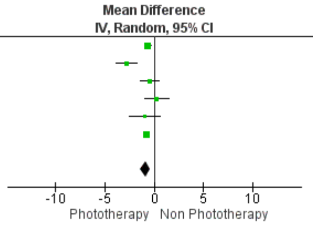


Fig. 8. [Pooled analysis results using a random effect model (forest plot): Malondialdehyde (nmol per ml) Excluding High and Low levels]

Study or Subgroup	Phototherapy Mean	SD	Total	Non Phototherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Random sequence generation (selection bias)
Abdellatif et al., 2012-b	2.44	0.6	25	3.07	0.52	25	27.1%	-0.63 [-0.94, -0.32]	Unclear risk
Gathwala, 2002	8.6	0.8	30	11.4	2.9	30	12.9%	-2.80 [-3.88, -1.72]	Unclear risk
Tekgundiz et al., 2016-a	9.9	1.48	56	10.35	3.39	56	14.4%	-0.45 [-1.42, 0.52]	Unclear risk
Tekgundiz et al., 2016-b	3.76	2.94	56	3.5	3.75	56	10.7%	0.26 [-0.99, 1.51]	Unclear risk
Tekgundiz et al., 2016-c	5.1	3.7	56	6.03	4.76	56	7.7%	-0.93 [-2.51, 0.65]	Unclear risk
Abdellatif et al., 2012-a	2.59	0.47	25	3.37	0.64	25	27.1%	-0.78 [-1.09, -0.47]	Unclear risk
Total (95% CI)			**248**			**248**	**100.0%**	**-0.85 [-1.36, -0.34]**	

Heterogeneity: Tau² = 0.22; Chi² = 17.47, df = 5 (P = 0.004); I² = 71%
Test for overall effect: Z = 3.27 (P = 0.001)



[Fig. 9. Pooled analysis results using a random effect model (forest plot): Malondialdehyde (nmol per liter)]

Study or Subgroup	Phototherapy Mean	SD	Total	Non Phototherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Random sequence generation (selection bias)
Mustafa et al., 2021	15.78	6.7	47	25.11	14.05	47	14.7%	-9.33 [-13.78, -4.88]	Unclear risk
Allam et al., 2017-a	15.6	10.9	41	10.9	8.3	41	15.2%	4.70 [0.51, 8.89]	Unclear risk
Allam et al., 2017-b	14.6	10.2	41	11.8	7.9	41	15.6%	2.80 [-1.15, 6.75]	Unclear risk
Awad, 2020	16.2	3.3	30	11.92	3.297	30	18.9%	4.28 [2.61, 5.95]	Unclear risk
Aycicek, 2007	16.34	7.4	49	11.34	5.9	57	17.7%	5.00 [2.42, 7.58]	Unclear risk
Dogan et al., 2011	10.85	6.4	36	11.1	3.84	36	17.9%	-0.25 [-2.69, 2.19]	Unclear risk
Total (95% CI)			**244**			**252**	**100.0%**	**1.42 [-1.95, 4.80]**	

Heterogeneity: Tau² = 15.00; Chi² = 41.05, df = 5 (P < 0.00001); I² = 88%
Test for overall effect: Z = 0.83 (P = 0.41)

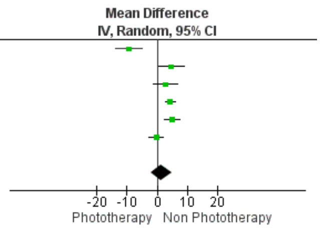


Fig. 10 [Fig. 10. Pooled analysis results using a random effect model (forest plot)]: Total Oxidative Stress

Study or Subgroup	Phototherapy Mean	SD	Total	Nonm Phototherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Random sequence generation (selection bias)
Erdam et al., 2011	9.4	1.5	36	8.4	1.8	36	8.1%	1.00 [0.23, 1.77]	Unclear risk
Kaplan, et al., 2005	18.08	4.5	41	19.08	5.6	41	3.6%	-1.00 [-3.20, 1.20]	Unclear risk
Midan et al., 2022-a	5.25	1.35	12	7.8	1.87	12	6.1%	-2.55 [-3.85, -1.25]	Unclear risk
Midan et al., 2022-b	5.1	1.25	40	8.2	1.8	40	8.4%	-3.10 [-3.78, -2.42]	Unclear risk
Ozutre, 2000	0.85	0.2	19	0.99	0.15	19	9.6%	-0.14 [-0.25, -0.03]	Unclear risk
Putra, 2018	53.05	10.18	30	23.73	8.2	30	1.1%	29.32 [24.64, 34.00]	Unclear risk
Sarici et al., 2015	7.52	0.79	62	7.72	0.75	62	9.5%	-0.20 [-0.47, 0.07]	Unclear risk
Shahaswari et al., 2017	3.76	0.23	35	2.8	0.18	35	9.7%	0.96 [0.86, 1.06]	Unclear risk
Sidrah et al., 2015	2.8	0.2	60	3.227	0.227	60	9.7%	-0.43 [-0.50, -0.35]	Unclear risk
Thaigarjan, 2010	13.79	2.85	40	12.61	2.32	40	6.7%	1.18 [0.04, 2.32]	Unclear risk
Aycicek, 2007	1.98	0.33	49	2.46	0.36	57	9.6%	-0.48 [-0.61, -0.35]	Unclear risk
Ayyapan et al., 2015	7.72	0.89	50	5.72	0.62	50	9.4%	2.00 [1.70, 2.30]	Unclear risk
Dogan et al., 2011	3.47	2.15	69	3.46	1.6	69	8.5%	0.01 [-0.62, 0.64]	Unclear risk
Total (95% CI)			**543**			**551**	**100.0%**	**0.20 [-0.33, 0.73]**	

Heterogeneity: Tau² = 0.76; Chi² = 983.79, df = 12 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.75 (P = 0.45)

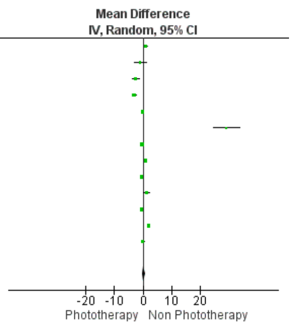
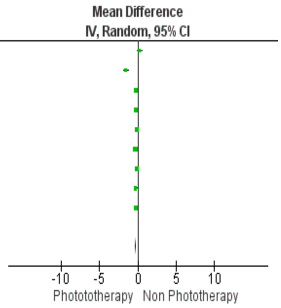


Fig.11[. Pooled analysis results of observational studies using a random effect model (forest plot): Malondialdehyde (nmol per ml)

Study or Subgroup	Phototherapy Mean	SD	Total	Non Phototherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Random sequence generation (selection bias)
Dogan et al., 2011	1.99	0.95	36	1.75	0.57	36	5.7%	0.24 [-0.12, 0.60]	Unclear risk
Kurban et al., 2014	4.26	0.57	40	5.8	0.95	40	6.1%	-1.54 [-1.88, -1.20]	Unclear risk
Mustafa et al., 2021	0.86	0.13	47	1.08	0.1	47	14.1%	-0.22 [-0.27, -0.17]	Unclear risk
Allam et al., 2017-a	0.28	0.16	41	0.53	0.36	41	12.4%	-0.25 [-0.37, -0.13]	Unclear risk
Allam et al., 2017-b	0.53	0.27	41	0.65	0.37	41	11.8%	-0.12 [-0.26, 0.02]	Unclear risk
Awad, 2020	0.48	0.02	30	0.77	0.134	30	14.1%	-0.29 [-0.34, -0.24]	Unclear risk
Aycicek, 2007	1.48	0.13	57	1.54	0.31	57	13.3%	-0.06 [-0.15, 0.03]	Unclear risk
Bulut, 2019-a	2.04	0.37	20	2.34	0.21	20	10.3%	-0.30 [-0.49, -0.11]	Unclear risk
Bulut, 2019-b	2.08	0.22	20	2.33	0.18	20	12.3%	-0.25 [-0.37, -0.13]	Unclear risk
Total (95% CI)			**332**			**332**	**100.0%**	**-0.27 [-0.38, -0.15]**	

Heterogeneity: Tau² = 0.02; Chi² = 86.07, df = 8 (P < 0.00001); I² = 91%
Test for overall effect: Z = 4.68 (P < 0.00001)



[Fig. 12. Pooled analysis results of observational studies using a random effect model (forest plot): Total Antioxidant Capacity]

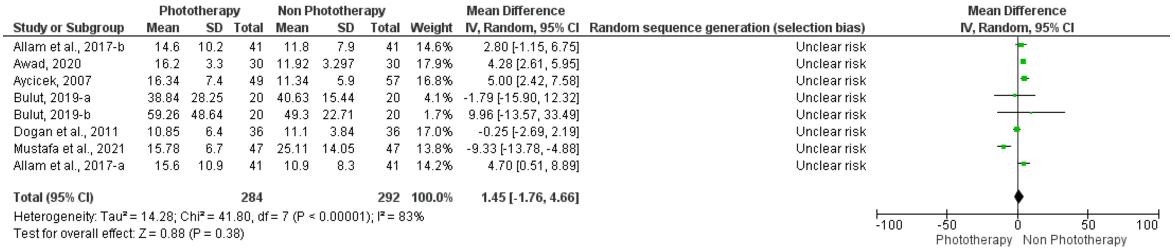


Fig.13. **[Pooled analysis results using a random effect model (forest plot): Total Oxidative Stress]**

Discussion

Neonatal hyperbilirubinemia can be managed using phototherapy, which has been proven to be a life-saving therapy (40)**.** NJ affects almost 70% of low birth weight new-borns in the first few days of life (40,41). Vulnerable new-borns like preterm babies and those suffering from congenital hemoglobinopathy typically have compromised antioxidant profiles and deficient immune response compared to their full-term counterparts.(9, 42,43,44). Recent studies have shown that phototherapy is responsible for DNA damage, oxidative stress, and proinflammatory cytokine release (30,32,37). Hence, this vulnerable population is prone to photo-oxidative side effects of phototherapy. There is a lack of consensus on the detrimental effects of phototherapy on the serum oxidative stress markers in the new-borns with hyperbilirubinemia. (4, 10, 19)**.**

Hemati, 2022 recently reported a meta-analysis proving the correlation of phototherapy with paediatric cancer and concluded that, phototherapy may be a risk factor for childhood cancer. According to this finding, strict adherence to scientific recommendations for bilirubin thresholds is indicated to reduce the unnecessary exposure to phototherapy. (19, 46)**,** Kiyoshi *et al.,* 2021 performed a meta-analysis to determine the potentially harmful effects of phototherapy on neonatal health. They concluded that jaundice and phototherapy were the likely prognostic factors for childhood-onset allergic diseases, though the associations were smaller than previously thought. (43). The meta-analyses were conducted by Liangliang *et al.,* 2021 and 2021. reported that a continuous phototherapy and intermittent phototherapy equally produce harmful effects (44) and home set up phototherapy can be more beneficial than hospital-based phototherapy in the NJ (45). These results are similar with the results of meta-analysis conducted by Anderson *et al.,* 2021 (46). Nizm *et al.,* 2020 where these efficacy of double phototherapy for preterm new-borns analysed. These studies concluded that the double surface phototherapy can give higher efficacy than single surface for varying gestational ages and birth weights but data regarding adverse effects were not reported (47). Result of meta-analysis by A Tridente *et al.,* 2011, indicated that there were no significant differences in the LED and conventional phototherapy in therapeutic efficacy for preterm new-born hyperbilirubinemia (48).

There are very few meta-analyses reporting the adverse effects of phototherapy in NJ. The present meta-analysis was carried out to examine the impact of phototherapy on oxidative stress markers and proinflammatory cytokines in the new-borns with hyperbilirubinemia. To assist paediatricians in treating NJ in the premature, low birthweight, and sensitive neonates, this meta-analysis may provide important clues.

It was evident in all the studies considered here in the new-borns enrolled were having a postnatal age between 1-15 days. All authors included full-term new-borns except Allam et al., 2017; Awad, 2020; Gathwala 2002; Kaplan, et al., 2005; Tekgundiz et al., 2016; who estimated the effect of phototherapy on preterm neonates. Shahaswari et al., 2017 had enrolled late preterm and Sidrah *et al.,* 2015 and Akisu,1998 had enrolled both preterm and full-term neonates.

After the analysis, it was found that MDA. TOS, TAC, TNF-α and IL-6 significantly changed after exposure to therapeutic phototherapy. Both The conventional type phototherapy and fluorescent light may produce oxidative stress and inflammatory cytokines elevation. (15) TNF-α elevation was invariably observed in all the neonates within 72 hours of exposure to phototherapy. However, the diversity of phototherapy devices, types of light sources and other exposure conditions were the confounding factors. It might be due to the non-adherence of the physicians to follow the guidelines related to phototherapy that these studies have a considerable variability. Oxidative stress parameters were elevated in the neonates exposed to phototherapy even when they were kept at 40 cm distance. The findings indicate a strong association of the modes of use of phototherapy devices and their correlation with untoward effects. It may be recommended that the duration of exposure should be intermittent to reduce the danger of heat, immune perturbance and infections as suggested in (48, 53). The result of this meta-analysis may help to generate up-to-date guidelines for the use of phototherapy and provide clues on using adequate sample sizes.

It is noteworthy that a study conducted by us in a small number of neonates with sickle cell anemia (44) indicated that these neonates have increased levels of pro-inflammatory cytokines and oxidative stress. However, the minimal sample size in this study was inadequate to draw any statistical conclusions. More systematic investigations using specific types of photo therapy with controlled variables x separately tested in healthy, premature neonates and new-borns with congenital disease may provide better insights into the vulnerabilities of these subgroups of the adverse effects of photo therapy.

Limitations

The meta-analysis had the following limitations: The studies included here in had limited sample size. The search for relevant articles was performed on the search engines yielding the literature only in English language. The heterogeneity among studies was also found to be high.

Conclusion

Phototherapy produces significant alterations in the oxidative stress parameters and proinflammatory cytokines in the exposed new-borns. more studies are required to draw a valid conclusion.

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