Melatonin for Neuroprotection in Neonatal Encephalopathy: A Systematic Review & Meta-Analysis of Clinical Trials.

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Abstract:

Objective: Melatonin has shown neuroprotective properties in pre-clinical studies of perinatal asphyxia through antioxidant, anti-apoptotic and anti-inflammatory actions. Studies have also demonstrated its safety and efficacy in neonatal encephalopathy (NE). However, its role in the current era of therapeutic hypothermia (HT) is unclear. The objective of this review is to describe the currently available clinical evidence for Melatonin as a potential therapy for NE.

Methods:

Data Sources: We searched Medline, EMBASE, CINAHL, LILACS, and Cochrane central databases, published journals, and conference proceedings from inception to 31st May 2020. **Study Selection:** Randomised controlled trials (RCTs) of Melatonin for NE in term or late preterm infants reporting neurodevelopmental outcomes, death, or both. The evidence quality was evaluated using the GRADE system, while the recommendations were taken according to the quality

Results: We included five RCTs involving 215 neonates. Long-term development outcome data is lacking in all except in one small study, reporting significantly higher composite cognition scores at 18 months. One study reported intermediate 6-month favorable development on follow-up. Meta-analysis of mortality in combined HT+ Melatonin group vs HT alone (Studies= 2, participants= 54) demonstrated no significant reduction with relative risk (RR) 0.42; 95%CI, 0.99-1.12). The overall GRADE evidence quality was very low for a very small sample size. We did not meta-analyze the data for Melatonin alone therapy without HT, as the included studies were of very low quality.

Conclusions: Despite strong experimental data supporting the role of Melatonin as a neuroprotective agent in NE (both alone and as an adjunct with therapeutic hypothermia), the clinical data supporting the neuroprotective effects in neonates is limited. Larger well designed, adequately powered multicentre clinical trials are urgently needed to define the neuroprotective role of Melatonin in optimizing outcomes of NE.

Keywords: hypoxic-ischemic encephalopathy (HIE), neonatal encephalopathy (NE), newborn, neuroprotection, Melatonin, therapeutic hypothermia (HT), level of evidence (LOE)

Abbreviations:

Amplitude integrated electroencephalography (aEEG), Hypoxic-ischemic encephalopathy (HIE), Hypoxia and ischemia (HI), therapeutic hypothermia (HT), level of evidence (LOE), Neonatal encephalopathy (NE), Magnitude resonance Imaging (MRI)

BACKGROUND:

Perinatal asphyxia accounts for nearly a quarter (23%) of neonatal mortality worldwide. The risk of adverse outcomes such as death, cerebral palsy, and neurosensory impairment can be as high as 50% in perinatal asphyxia. [1] The risk is highest with severe stage 3- (100%) and moderate stage 2- (33%) neonatal encephalopathy (NE) survivors. [2] Last decade has seen impressive progress in the management of asphyxia with the introduction of therapeutic hypothermia (HT). With the current practice of HT, there has been a promising reduction in the mortality of NE from 25% to 9% and the disability from 20% to around 16% along with a reduction in the rate of cerebral palsy. [3,4] However, not all children benefit from treatment, and intellectual impairment may persist even in the absence of cerebral palsy. [5] Moreover, a subset of NE population such as neonates born to chorioamnionitis mothers, preterm, or those presenting beyond the therapeutic window of HT, is less likely to be benefitted. [6] There is also concern that HT may not reduce mortality or may worsen the outcome in low and middle-income countries in the presence of sepsis. [7] Therefore, different adjuvant therapies like erythropoietin[8], magnesium[9], allopurinol[10], xenon[11], and Melatonin[12] either alone or in combinations with HT, are being actively explored in clinical trials to improve outcomes in NE.

Melatonin, produced by the pineal gland, has favorable pharmacokinetics, an excellent safety profile, and is widely available. It renders neuroprotection through its strong anti-apoptosis properties by both receptor-mediated signalling (transmembrane receptors MT1 and MT2, Cytosolic receptor MT3 and a nuclear receptor) and directly non-receptor mediated antioxidant and free radical scavenger action. [12] It can easily cross the blood-brain barrier and reach the intracellular compartment, providing neuroprotection at the cellular level in hypoxia ischemia (HI). Melatonin has anti-inflammatory and antioxidant properties that decrease microglial and

astrocyte proliferation and promote subsequent myelination within the white matter. It also has anti-excitatory effects through the modulation of gamma-aminobutyric acid and glutamate (GABA) receptors. Additionally, it is also known to improve mitochondrial integrity upregulates antioxidant enzymes, a step important for the prevention of the release of apoptotic mitochondrial enzymes, seen in the secondary phase of neuronal damage in HI. [7,12] Melatonin, due its multifaceted neuroprotective mechanism, has the unique potential to limit damage duirng the latent phase (6-15 hours after HI and reperfusion injury) and reduce the secondary phase of neuronal death, associated with secondary energy failure. Melatonin also attenuates continuing brain injury, seen in the tertiary phase that can result in a reduction in neurons and plasticity of the brain. [7,13]

Melatonin crosses all physiological barriers such as the blood-brain and the placenta; melatonin has an excellent safety profile.[14,15] Pineal melatonin production is not fully mature at birth, even in term infants for 2-4 months, producing a transient melatonin deficiency at birth, which makes the newborn furthermore susceptible to oxidative damage in the event of the stress of NE. [16] Melatonin is considered to be the most promising neuroprotective agent amongst the 13 candidate therapies considered for postnatal neuroprotection of NE. [17] There is compelling animal experiment data regarding its neuroprotective efficacy in reducing brain injury by reducing apoptosis, inflammation, and lipid peroxidation. It is also shown to reduce the severity of cerebral palsy in rats [18,19]. The objective of this systematic review (SR) is to evaluate if neonates with Hypoxic-ischemic encephalopathy (HIE) or neonatal encephalopathy (NE) *(Population)* treated with Melatonin (any dose or route of administration) *(Intervention)* as compared to standard therapy (either supportive therapy *or* HT *or* magnesium *or* erythropoietin *or* any combination) *(Comparison)*, have reduced mortality *or* better neurodevelopment outcome on follow up at 18-24 months of age *(Outcome).*

MATERIAL AND METHODS

This SR and meta-analysis were conducted and reported as per the guidelines from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses). The following were criteria for the inclusion of the study for this SR.

Criteria for study selection:

(**1) Study Selection:** Only randomized controlled trials (RCTs) and quasi-randomized were eligible for inclusion. Case-control or cohort studies, case reports/series, letters to editors, editorials, review articles, and commentaries were identified for potential studies and reviewed for relevant data, however, excluded for the SR and meta-analysis. Duplicate reports not providing additional information were also excluded.

(2) Type of participants:

Neonates (term or late preterm infants) fulfilling criteria for perinatal asphyxia or Neonate with NE due to perinatal asphyxia which is as follows: (i) profound metabolic or mixed acidaemia (pH <7.00) in an umbilical artery blood sample, if obtained, (ii) persistence of an Apgar score of 0–3 for longer than 5 min, (iii) neonatal neurologic sequelae (e.g., seizures, coma, hypotonia), and (iv) multiple organ involvement (e.g., kidney, lungs, liver, heart, intestines) [20].

(**3) Type of intervention:**

1) Melatonin (regardless of dose, duration, and route of administration) *vs* placebo or

2) Melatonin as an adjuvant to therapeutic hypothermia (HT) *vs* HT alone or

3) Melatonin, along with erythropoietin *or* magnesium sulfate, *or* a combination of two *or* more of the therapies which are established for the treatment of perinatal asphyxia *versus* controlled arm.

(4) Outcomes:

Primary Outcomes:

1. Neurodevelopment impairment (NDI) as any form of change assessed at 18-24 months (by any standardized, validated tool like Bayley 2 or 3 (BSID), Griffith, etc.)

2. Death before discharge (due to any cause) (early or late neonatal death).

Secondary:

1. Cerebral palsy (CP) or unilateral deafness or unilateral blindness diagnosed on or before 24 months of age (as defined by the authors)
2. Neurodevelopment delay: as one or more of the following i) BSID III score in any domain (e.g. cognitive/motor /language/ social/ adaptive score > 1SD or >2 SD below the normative mean or ii) BSID II MDI and/or PDI scores >1 SD or >2 SD below the normative mean; iii) non-ambulant CP (GMFCS level 3-5); iv) blindness bilateral v) sensorineural deafness requiring amplification. Any other clinically important outcome was reported by authors (not pre-specified).
3. MRI and EEG finding at follow up
4. Persistent Seizures disorder
5. Biomarkers of brain injury such as S100-B.

Review Methods:

Literature search Strategy:

The Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), LILACS, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched applying the combinations of controlled vocabulary (e.g., MeSH/Emtree) and free text words guided by our PICO parameters. No language restriction was applied. The details of search terms, including the search strategies for individual databases, are available in *Supplemental Information*. Google search has also been conducted to minimize publication bias. The search was conducted for the period between inception till 31st May 2020.

Data extraction: Author AKP conducted the initial search in all the databases, and the final list was assimilated. JA screened all titles and abstracts to determine the relevance to full-text eligibility. JA and KM conducted data extraction independently, and inconsistencies were resolved by discussion and involving NR. The studies' original authors were contacted for any further clarifications and/or additional missing data if needed.

Assessment of risk of bias:

For randomized studies, we used the Cochrane Handbook 'Risk of Bias assessment tool [21]. Quality assessment of the included studies was done independently by two authors (JA and KM). Differences of opinion were resolved by discussion and involvement with NR.

Data Synthesis and Statistical analysis: We performed statistical analysis using Review Manager 5.4 (Cochrane Collaboration) and used the Cochrane Random-effects model for the Meta-analysis. A two-tailed P value of <0.05 was considered statistically significant. The results of the meta-analysis and summary of findings are provided with the Cochrane Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the level of evidence (LOE). [22] The authors (JA and KM) evaluated independently the level of

228 evidence using the GRADE approach. The discrepancies were resolved by discussion and
229 consensus and with the involvement of NR.

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RESULTS:

Description of studies:

The result of the literature search and study selections is shown in the PRISMA flow diagram in ***Figure 1***. An initial database search identified 614 records, 564 studies were manually screened after duplicate removal, and only 5 RCT fitting the inclusion criteria were included [23–27]. The baseline characteristics of the five included studies, encompassing 215 neonates are reported in ***Table 1*.**

Risk of bias (ROB) among included studies:

The results of the ROB assessment of the included studies are presented in ***Figure 2***. Overall, all studies had a high risk of performance biased (4/5) and a low risk of attrition and reporting bias. Only 2/5 studies have proper randomization, and all were at unclear risk of selection bias due to unclear allocation concealment. Lack of use of HT in the control group, which is the current standard of care in three-quarters of the studies has generated baseline *other bias* in 3/5 studies.

Primary Outcome:

1. **Neurodevelopment impairment (NDI):** Only one study by Calero AJ et al.[27], reported development at 18 months showing composite cognitive score, significantly higher ($p < 0.05$) in the Melatonin and HT group. However, there were no statistical differences in the cognitive scale at six months or for the other components of neurologic development (language and motor skills) at 6 and 18 months. Aly H et al. [26] performed follow up until six months, however, reported significantly better normal neurological examination by the Denver Development screening test (DDST II) in the melatonin group (*Table 1).*

2. **Death** in the neonatal period is reported by four studies[24–27]. Meta-analysis of the mortality in combined HT+ Melatonin group vs HT alone (RR0.42, [95% CI 0.99-1.12], Studies 2, participants=54, I^2=0) was not significant. We GRADE the Level of evidence (LOE) of this to be very low for a very small sample size. We did not pool the data for melatonin alone therapy without HT, as the included studies were of very low quality. *(Figure3,4)*

Secondary Outcomes:

No study described long term clinical follow-up findings such as cerebral palsy, neurodevelopment impairment, deafness, and blindness. El Farargy et al. [23], observed that the biochemical marker of neuronal injury, Serum S100-B concentrations, which correlates with the severity of HIE, was significantly reduced on Day 2 & 6 of the intervention group (Magnesium and Melatonin group) suggesting a synergistic effect of magnesium and Melatonin in neuroprotection. Aly H et al. [26], reported no difference in grey matter abnormality; however, the white matter abnormalities were reduced in the melatonin+ HT group (P=0.014) on follow-up MRI. Although the baseline EEG and follow up EEG after two weeks did not differ much, the intervention group (melatonin/HT group) had less clinical seizures (P=0.032). In contrast, Calero et al. [27], found no difference in MRI or amplitude-integrated EEG (aEEG) between treatment groups.

Discussion:

This SR highlights the clinical knowledge gap in the use of melatonin for neuroprotection in NE despite supportive pre-clinical and animal data. There is a dearth of clinical data on long-term neurodevelopment outcome of melatonin therapy in NE. Melatonin's role as an additional supportive therapy in NE without HT requires further exploration in better designed clinical trials; currently, available evidence is from a small number of low-quality studies. The meta-analysis of melatonin as an adjunct therapy to HT in NE did not reveal benefit for mortality. However, caution must be exercised in the interpretation of this result due to the very small sample size, and this LOE is GRADED as very low.

The strengths of this SR include a comprehensive search strategy across multiple databases and the evaluation of multiple clinically relevant outcomes. The limitation of the review is due to limited numbers of small studies, high risk of bias in some of the included studies, different doses and dosing regimens of melatonin used, little pharmacokinetic data with no target therapeutic range, and a paucity of long-term neurodevelopment follow up data.

Melatonin is considered safe in the neonatal population with minimal side effects, even in higher doses; side effects are limited to its hypnotic and sedative properties [28]. Melatonin is available in many countries without prescription as a nutritional supplement. Neonatal clinical literature has described melatonin doses ranging from 0.5 mg/kg for sedation to as high as 10mg/kg/dose for neuroprotection without any serious adverse events or interaction with other medications [16]. Oral Melatonin has rapid absorption but low bioavailability (ranges from 3-15%) with great inter-individual variability mainly attributed to high first-pass hepatic metabolism. The intravenous formulation has higher bioavailability by bypassing the first-pass metabolism in the liver. The plasma level needed for melatonin's neuroprotective effects in babies is unclear but is likely to be supraphysiological for maximal free radical protection [15,29].

From pre-clinical studies in piglets, a therapeutic range of 15-30 mg/L is safe and optimal for neuroprotection when melatonin is added to HT after transient HI [30]. This level is achieved with doses of 20-30mg/kg every 24h in the piglet; similar doses are likely to be required in babies, although neonatal pharmacokinetic studies are needed. Future studies must incorporate therapeutic drug level monitoring, to ensure bioavailability and understand interindividual variation, and the effect of HT [15]. The therapeutic window for neuroprotection offered by melatonin appears to be limited (10 minutes to 2 h after HI), as shown in the animal studies. Hence, melatonin should be administered as early as possible to achieve the therapeutic levels for better neuroprotection [19,30]. Although no definite melatonin neuroprotective protocol can be recommended presently, pre-clinical studies suggest a melatonin dose of 20-30mg/kg given as soon as possible, after birth. [31] Two relevant studies NCT03806816 (MELPRO trail) and NCT02621944 may be able to answer some of these pharmacokinetic, safety, and clinical outcome questions in the future.

As melatonin is sparingly soluble in aqueous vehicles, solubility enhancers, such as ethanol, have been used, to obtain a solution with the desired concentration. The use of ethanol as an excipient could have been a confounding factor in previous pre-clinical [32–34] and clinical studies, including the study by Fulia 2001 included in this SR where melatonin was dissolved in a 1:90 mixture of ethanol:0.9% saline. [24] Low doses of ethanol can have neuroprotective effects against ischemia/reperfusion injury [35] and also may have an effect on GABA expression and increase GABAergic neurotransmission. [36] Babies in the neonatal intensive care around the world are commonly exposed to potentially neurotoxic excipients, including ethanol; efforts are urgently needed to understand pharmacokinetics, long-term effects, and safety of ethanol in excipients and potentially reduce this exposure. [37] A high concentration intravenous melatonin formulation with excipients safe for babies is urgently needed. [30]

This SR also draws attention to some limitations of the included studies. Fulia et al. [24] and Farargy et al. [23] focused on biochemical markers of lipid peroxidation without reporting clinical outcomes. The feasibility trial by Aly et al. [26], had only six months of follow-up and included more severe NE cases in the control arm. Calero et al.[27] had very few subjects and described development at 18 months, but cerebral palsy, neurosensory impairments were not reported. Ahmad et al. [25], included the milder cases of NE in their study; mortality was reduced in moderate and severe NE cases after removing the milder cases. The result of this study needs to be interpreted cautiously due to the high risk of bias and as enrolment of the subjects was entirely based on clinical examination. Only one study used a combination of magnesium and melatonin; although a reduction in markers of neuronal injury was observed, the study did not report clinical outcomes [23], thus limiting its clinical utility. We did not find any clinical study comparing the efficacy of the combination of melatonin and erythropoietin for neuroprotection, although a pre-clinical study has reported this combination recently. [31] Melatonin has the potential to act synergistically with other therapeutic agents as pathways of neuroprotection differ between therapeutics, for example, HT decreases metabolic rate, prevents secondary energy failure and apoptosis [2], magnesium sulfate has anti-inflammatory properties and competitively antagonizes calcium ion entry in the NMDA channel [9], erythropoietin has neurotropic and anti-apoptotic properties, and stimulates neurogenesis and oligodendrogenesis [8]. It is also important to consider the timing of therapies with early melatonin targeting the high levels of oxygen free radicals in the minutes and hours after birth in NE.

Several proposed trials for maternal supplementation of Melatonin for fetal neuroprotection have been published in the last decade; however, we could find no published reports of these trials. Thus, no conclusion about antenatal supplementation of melatonin for fetal neuroprotection can be drawn. [38–41]

The deficiency of our current knowledge, highlighted in this review, should pave the way for future clinical studies, addressing the limitation of the present studies. Larger powered safety and efficacy clinical studies of HT with intravenous melatonin reaching therapeutic melatonin levels are urgently needed. Important and relevant clinical measures such as long term neurodevelopment outcomes and surrogate markers of a brain injury such as conventional MRI, proton magnetic resonance spectroscopy (peak area ratio of Lactate/N Acetyl aspartate (Lac/NAA)), and amplitude-integrated EEG (aEEG) must be used for prediction of neurological outcome and comparability with other standards of care. [42,43]

In conclusion, despite promising pre-clinical data and encouraging clinical data about the role of melatonin in the treatment of NE, this SR highlights the paucity of large, high-quality RCTs of melatonin as either alone or an adjunct therapy with HT (with adequate melatonin therapeutic levels, sample size, and appropriate surrogate outcome measures). It is clear that clinical studies of melatonin as a neuroprotective agent significantly lag behind the promising pre-clinical studies. The translational pipeline, taking therapies from bench to bedside, has therefore stalled at the stage of Phase I and II clinical trials. This translational gap requires researchers, pharmaceutical companies, funding bodies, and clinicians to work together so that many more neonates with NE can have the opportunity to benefit from this potentially safe and effective therapeutic agent and thus be saved from lifelong disabilities.

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Figure 1: PRISMA flow diagram for literature search

Figure 2: Risk of Bias (ROB) assessment of included studies:

Figure 3: Meta-analysis for mortality in Melatonin with therapeutic hypothermia (HT+M) vs therapeutic hypothermia alone (HT)

Fig 4: Grade recommendations of the quality of evidence

Study (yr)	**Design**	**Participants** (Sample size)	**Intervention (Dose) (Diluent detail)**	**Comparison**	**Primary Outcome**	**Secondary outcome**
1.Fulia et al (2001) (USA)	RCT	Term (N=20)	M (oral) 10 mg/2 hourly 8 doses (80 mg total) (n=10) dissolved in a 1:90 mixture of ethanol:0.9% saline	SC	1) ND: NA 2) Mortality: M= 0/10 *vs* SC=3/10 in control RE:0.14 [95% CI,0.01- 2.45]	NA
2.Aly H et al. (2015) (Egypt)	RCT	Term (N=30)	HT + M (oral) 10mg/kg daily for a total of five doses (n=15) Melatonin tablets (1 or 3mg/tablet; Puritan's Pride, Oakdale, NY, USA) were crushed, then dissolved in 5ml of distilled water and administered via an orogastric tube.	HT: Manual Cooling with ice packs (n=15)	ND: long term follow up: Nil Mortality: 1/15 in HT+M vs 4/15 death HT (P=0.33) RE: 0.25 [95% CI,0.03-1.98]	at 6 months: Significant improve survival without disability at 6 months in HT+M (10/14 vs 3/11 normal neurological examination and DDST) (P< 0.001). HT+M fewer clinical seizures and less white matter abnormalities on MRI.
3.Ahmad QM (2018) (Pakistan)	RCT	Term or late preterm (clinical features of HIE) (N=80)	M (Oral) 10 mg single dose at admission (n=40) (Information on diluent not available)	SC (n=40)	1) ND: NA 2) Mortality: M = 5/34(12.5%) death ,SC=14/36 (35%) (p=0.03) (*in moderate and severe HIE case*) RE:0.38 [95% CI, 0.15-0.94]	NA
4.El Farargy et al (2019)	RCT	Term or late preterm (N=60)	M + Magnesium (n=30)	M (10 mg/kg daily enteral for 5 days). (n=30)	1) ND; NA 2) Mortality: NA	Both groups have lower concentration of S100-B on 6th day from baseline

(Egypt)			Information on diluent not available.			
5.Calero AJ et al (2020) (Spain)	RCT	Term or late preterm (N=25)	HT + M (n= 12) (IV melatonin 5mg/kg for 3 days) Information on diluent not available.	HT (n=13)	1)ND: Significant difference in Composite Cognitive score at 18 months, in HT+M , in BSID-3 no difference in other scores 2) Mortality: HT+M=1/12 vs. HT=1/13 (NS) RE:1.00 [95% CI, 0.07- 14.21]	No difference in aEEG /clinical seizures or MRI

Table 1: Characteristics of included studies

Yr: Years HT= therapeutic hypothermia, M= Melatonin, SC= Supportive care, IV = Intravenous, ND: neurodevelopment, DDST = Denver development screening test ,NA=not available , BSID-3 = Bayley Scale of infant development-3, RE= random effect , CI= Confidence interval , N= total sample size , n= number of subjects in Melatonin group

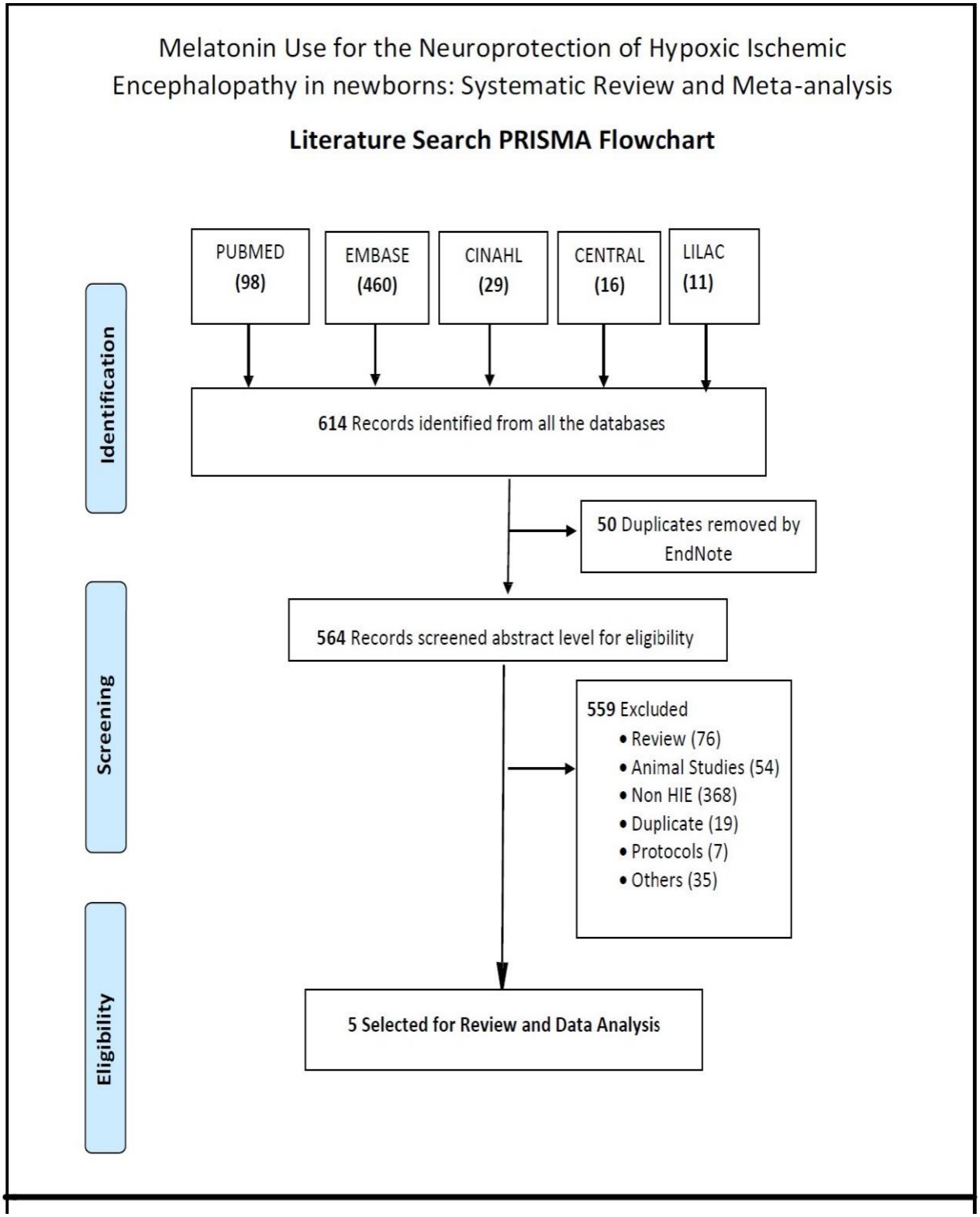

Figure 1: PRISMA flow diagram for literature search

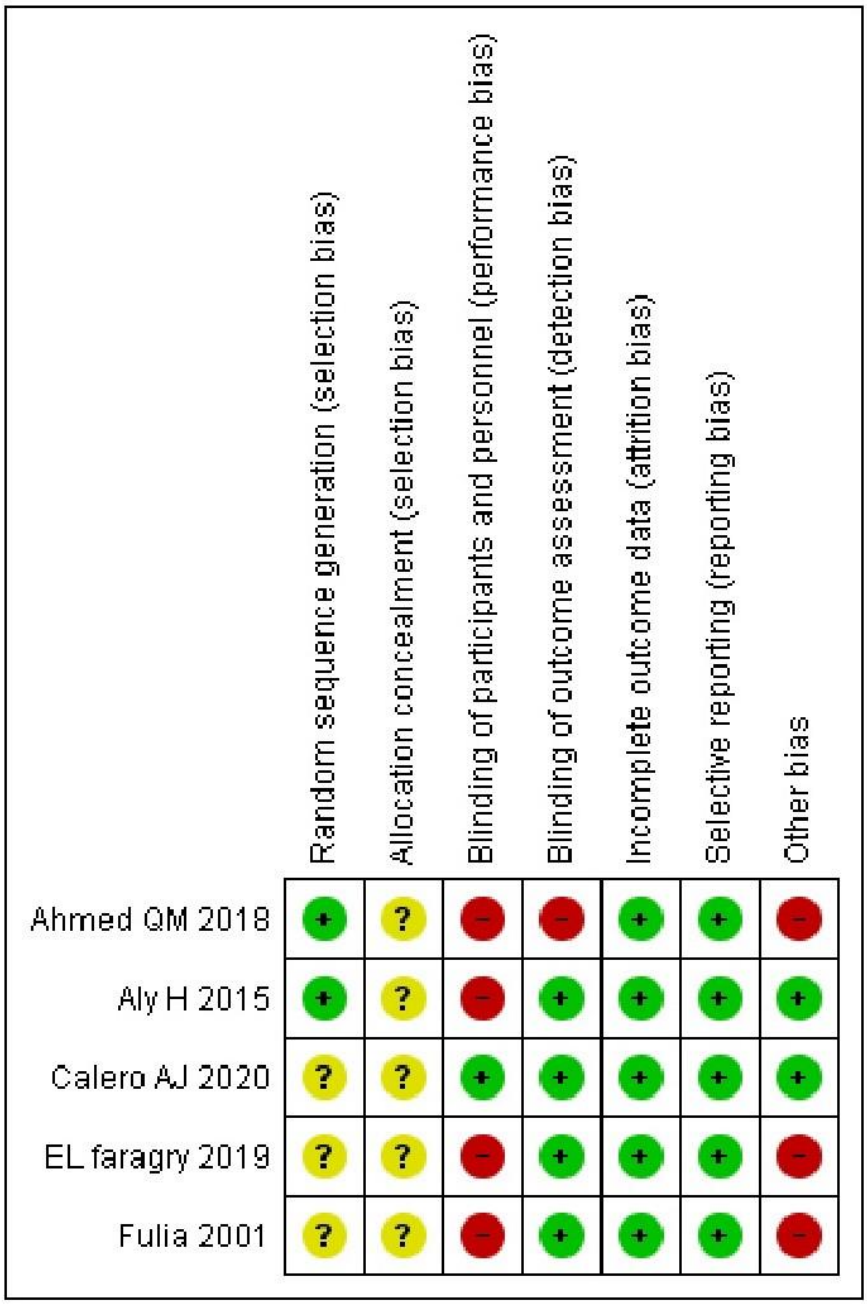

Figure 2: Risk of Bias (ROB) assessment of included studies:

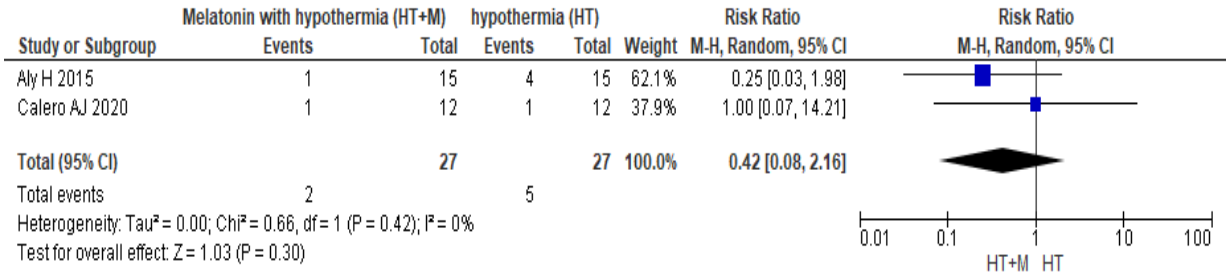

Figure 3: Meta-analysis for mortality in Melatonin with therapeutic hypothermia (HT+M) *vs* therapeutic hypothermia alone (HT)

For Melatonin for Neuroprotection in HIE*:*

Question: Mortality in combined Hypothermia+ melatonin *vs.* therapeutic hypothermia alone in HIE
Setting:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mortality in combine HT+Melatonin vs HT alone	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality in therapeutic hypothermia with Melatonin (follow up: median 28 days)												
2	randomised trials	serious [a]	not serious	not serious	serious [a]	publication bias strongly suspected [a]	2/27 (7.4%)	5/27 (18.5%)	**RR 0.42** (0.08 to 2.16)	**107 fewer per 1,000** (from 170 fewer to 215 more)	⨁◯◯◯ VERY LOW	

Fig 4: Grade recommendations of the quality of evidence

Supplemental Information

Search Strategies: Use of Melatonin for Hypoxic ischaemic brain injury
Advance Literature Search via PubMed/Embase/Cinahl/CENTRAL
April 17 2020

Study objective: To find out the effect of **melatonin** as adjunct therapy on newborns with hypoxic ischaemic encephalopathy.

Publication Use: meta-analysis of RCTs

Step 2: Please identify PICO terms from the question you formulated in step 1 above

- **(P) Neonates** AND Hypoxic ischemic encephalopathy
- **(I) Melatonin**
- **(C)Placebo or hypothermia**
- **(O)**
- **(T) Randomized Controlled Trials**
  Limits: (infants ≥ age 18 months)

Step 3: Please identify search concept/terms from PICO on step 2

Each concept combine → with AND Similar concept combine with OR	**Concept 1** **Synonyms/related words** ↓	AND	**Concept 2** **Synonyms/related words**	AND	**Concept 3** **Synonyms/related words**	AND	**Concept 4** **Synonyms/related words**
keyword	**Hypoxic ischemic encephalopathy**		**Melatonin**		**neonates**		Randomized Controlled Trial
OR	Neonatal hypoxia-ischaemia OR neonatal hypoxia-ischemia	**AND**	N-acetyl-5-methoxytryptamine	**AND**	Newborn	**AND**	Clinical Trials
OR	asphyxia		ramelteon		infants		**RCT**
OR	hypoxic-ischaemic encephalopathy		indolamine		late preterm		Controlled Clinical Trials
OR	HI				term		Random Allocation
OR	HIE				preterm		Multicenter studies
OR	perinatal hypoxia-ischemia				newborns		Control groups
OR	encephalopathy						Evaluation studies
OR	neonatal asphyxia						Randomized-Controlled
OR	perinatal hypoxic-ischemic brain injury						Randomized
OR	cerebral asphyctic events						Trial
OR	Hypoxia-Ischemia, Brain						

OR	hypoxia' OR 'hypoxic' OR 'asphyxia' OR 'hypoxic-ischemic encephalopathy' OR 'perinatal asphyxia' OR 'birth asphyxia' OR 'ischemia'						
OR	Brain Ischemia OR Hypoxia-Ischemia, OR Brain Ischemia OR Hypoxia Asphyxia						
OR	Neonatal Hypoxic-ischemic encephalopathy						
OR	Asphyctic						

Advanced literature search via PubMed /Embase/Cinhal/Central/Lilac

Database: Medline/PubMed Date

	Database Name: Medline/PubMed covered from 1966 to 17 April 2020	
#1	((((((((((((("hypoxic ischaemic encephalopathy"[All Fields] OR "hypoxia-ischemia, brain"[MeSH Terms] OR ("hypoxia-ischemia"[All Fields] AND "brain"[All Fields]) OR "brain hypoxia-ischemia"[All Fields] OR ("hypoxic"[All Fields] AND "ischemic"[All Fields] AND "encephalopathy"[All Fields]) OR "hypoxic ischemic encephalopathy"[All Fields]) OR (("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields]) AND ("hypoxic ischaemic encephalopathy"[All Fields] OR "hypoxia-ischemia, brain"[MeSH Terms] OR ("hypoxia-ischemia"[All Fields] AND "brain"[All Fields]) OR "brain hypoxia-ischemia"[All Fields] OR ("hypoxic"[All Fields] AND "ischemic"[All Fields] AND "encephalopathy"[All Fields]) OR "hypoxic ischemic encephalopathy"[All Fields]))) OR ((("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields]) AND hypoxia-ischaemia[All Fields]) OR (("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields]) AND hypoxia-ischemia[All Fields]))) OR ("asphyxia"[MeSH Terms] OR "asphyxia"[All Fields])) OR ("hypoxic ischaemic encephalopathy"[All Fields] OR "hypoxia-ischemia, brain"[MeSH Terms] OR ("hypoxia-ischemia"[All Fields] AND "brain"[All Fields]) OR "brain hypoxia-ischemia"[All Fields] OR ("hypoxic"[All Fields] AND "ischemic"[All Fields] AND "encephalopathy"[All Fields]) OR "hypoxic ischemic encephalopathy"[All Fields])) OR (HIE[All Fields] OR ("history"[Subheading] OR "history"[All Fields] OR "hi"[All Fields]))) OR (perinatal[All Fields] AND hypoxia-ischemia[All Fields])) OR ("brain diseases"[MeSH Terms] OR ("brain"[All Fields] AND "diseases"[All Fields]) OR "brain diseases"[All Fields] OR "encephalopathy"[All Fields])) OR ("asphyxia neonatorum"[MeSH Terms] OR ("asphyxia"[All Fields] AND "neonatorum"[All Fields]) OR "asphyxia neonatorum"[All Fields] OR ("neonatal"[All Fields] AND "asphyxia"[All Fields]) OR "neonatal asphyxia"[All Fields])) OR (perinatal[All Fields] AND ("hypoxic ischaemic brain injury"[All Fields] OR "hypoxia-ischemia, brain"[MeSH Terms] OR ("hypoxia-ischemia"[All Fields] AND "brain"[All Fields]) OR "brain hypoxia-ischemia"[All Fields] OR ("hypoxic"[All Fields] AND "ischemic"[All Fields] AND "brain"[All Fields] AND "injury"[All Fields]) OR "hypoxic ischemic brain injury"[All Fields]))) OR (("cerebrum"[MeSH Terms] OR "cerebrum"[All Fields] OR "cerebral"[All Fields] OR "brain"[MeSH Terms] OR "brain"[All Fields]) AND asphyctic[All Fields] AND events[All Fields])) OR ("hypoxia-ischemia, brain"[MeSH Terms] OR ("hypoxia-ischemia"[All Fields] AND	2776539

	"brain"[All Fields]) OR "brain hypoxia-ischemia"[All Fields] OR ("hypoxia"[All Fields] AND "ischemia"[All Fields] AND "brain"[All Fields]) OR "hypoxia ischemia, brain"[All Fields])) OR (("hypoxia"[MeSH Terms] OR "hypoxia"[All Fields]) OR ("hypoxia"[MeSH Terms] OR "hypoxia"[All Fields] OR "hypoxic"[All Fields]) OR ("asphyxia"[MeSH Terms] OR "asphyxia"[All Fields]) OR ("hypoxic ischaemic encephalopathy"[All Fields] OR "hypoxia-ischemia, brain"[MeSH Terms] OR ("hypoxia-ischemia"[All Fields] AND "brain"[All Fields]) OR "brain hypoxia-ischemia"[All Fields] OR ("hypoxic"[All Fields] AND "ischemic"[All Fields] AND "encephalopathy"[All Fields]) OR "hypoxic ischemic encephalopathy"[All Fields]) OR (perinatal[All Fields] AND ("asphyxia"[MeSH Terms] OR "asphyxia"[All Fields])) OR ("asphyxia neonatorum"[MeSH Terms] OR ("asphyxia"[All Fields] AND "neonatorum"[All Fields]) OR "asphyxia neonatorum"[All Fields] OR ("birth"[All Fields] AND "asphyxia"[All Fields]) OR "birth asphyxia"[All Fields]) OR ("ischaemia"[All Fields] OR "ischemia"[MeSH Terms] OR "ischemia"[All Fields]))) OR (("hypoxia"[MeSH Terms] OR "hypoxia"[All Fields]) OR ("hypoxia"[MeSH Terms] OR "hypoxia"[All Fields] OR "hypoxic"[All Fields]) OR ("asphyxia"[MeSH Terms] OR "asphyxia"[All Fields]) OR ("hypoxic ischaemic encephalopathy"[All Fields] OR "hypoxia-ischemia, brain"[MeSH Terms] OR ("hypoxia-ischemia"[All Fields] AND "brain"[All Fields]) OR "brain hypoxia-ischemia"[All Fields] OR ("hypoxic"[All Fields] AND "ischemic"[All Fields] AND "encephalopathy"[All Fields]) OR "hypoxic ischemic encephalopathy"[All Fields]) OR (perinatal[All Fields] AND ("asphyxia"[MeSH Terms] OR "asphyxia"[All Fields])) OR ("asphyxia neonatorum"[MeSH Terms] OR ("asphyxia"[All Fields] AND "neonatorum"[All Fields]) OR "asphyxia neonatorum"[All Fields] OR ("birth"[All Fields] AND "asphyxia"[All Fields]) OR "birth asphyxia"[All Fields]) OR ("ischaemia"[All Fields] OR "ischemia"[MeSH Terms] OR "ischemia"[All Fields]))) OR (("brain ischaemia"[All Fields] OR "brain ischemia"[MeSH Terms] OR ("brain"[All Fields] AND "ischemia"[All Fields]) OR "brain ischemia"[All Fields]) AND ("hypoxia-ischemia, brain"[MeSH Terms] OR ("hypoxia-ischemia"[All Fields] AND "brain"[All Fields]) OR "brain hypoxia-ischemia"[All Fields] OR ("hypoxia"[All Fields] AND "ischemia"[All Fields] AND "brain"[All Fields]) OR "hypoxia ischemia, brain"[All Fields]) AND ("ischaemia"[All Fields] OR "ischemia"[MeSH Terms] OR "ischemia"[All Fields]) AND ("hypoxia"[MeSH Terms] OR "hypoxia"[All Fields]) AND ("asphyxia"[MeSH Terms] OR "asphyxia"[All Fields]))----------	
#2	("melatonin"[MeSH Terms] OR "melatonin"[All Fields]) OR ("ramelteon"[Supplementary Concept] OR "ramelteon"[All Fields]) OR ("indolamine"[Supplementary Concept] OR "indolamine"[All Fields])----------	26416

#3	("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonates"[All Fields]) OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "newborn"[All Fields]) OR ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields]) OR (late[All Fields] AND preterm[All Fields]) OR ("term birth"[MeSH Terms] OR ("term"[All Fields] AND "birth"[All Fields]) OR "term birth"[All Fields] OR "term"[All Fields]) OR preterm[All Fields]----------	2422446
#4	#1 AND #2 AND #3----------	368
#5	(RCT[All Fields] AND ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trials"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]) AND ("controlled clinical trial"[Publication Type] OR "controlled clinical trials as topic"[MeSH Terms] OR "controlled clinical trials"[All Fields])) OR ("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields]) OR ("multicenter study"[Publication Type] OR "multicenter studies as topic"[MeSH Terms] OR "multicenter studies"[All Fields] OR "multicentre studies"[All Fields]) OR ("control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields]) OR ("evaluation study"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation studies"[All Fields])----------	2186559
#6	#4 AND #5----------	98
	Embase Session Results 17th April 2020	
#1	'hypoxic ischemic encephalopathy'/exp OR 'hypoxic ischemic encephalopathy' OR 'neonatal hypoxia-ischaemia' OR 'neonatal hypoxia-ischemia asphyxia' OR 'hypoxic-ischaemic encephalopathy'/exp OR 'hypoxic-ischaemic encephalopathy' OR hi OR hie OR 'perinatal hypoxia-ischemia' OR 'encephalopathy'/exp OR encephalopathy OR 'neonatal asphyxia'/exp OR 'neonatal asphyxia' OR 'perinatal hypoxic-ischemic brain injury' OR 'cerebral asphyctic events' OR asphyctic OR 'hypoxia-ischemia, brain'/exp OR 'hypoxia-ischemia, brain' OR 'hypoxia'/exp OR hypoxia OR 'hypoxic' OR 'asphyxia'/exp OR 'asphyxia' OR 'hypoxic-ischemic encephalopathy'/exp OR 'hypoxic-ischemic encephalopathy' OR 'perinatal asphyxia'/exp OR 'perinatal asphyxia' OR 'birth asphyxia'/exp OR 'birth asphyxia' OR 'ischemia'/exp OR 'ischemia' OR 'brain ischaemia'/exp OR 'brain ischaemia' OR 'hypoxia-ischemia' OR 'brain ischemia'/exp OR 'brain	3,029,945

	ischemia' OR (('brain'/exp OR brain) AND ('ischemia'/exp OR ischemia)) OR 'hypoxia asphyxia' OR 'neonatal hypoxic-ischemic encephalopathy'	
#2	'melatonin'/exp OR melatonin OR 'n-acetyl-5-methoxytryptamine'/exp OR 'n-acetyl-5-methoxytryptamine' OR 'ramelteon'/exp OR ramelteon OR 'indolamine'/exp OR indolamine	148,206
#3	neonates OR newborn OR infants OR 'late preterm' OR term OR preterm OR newborns OR infant OR neonate	2,908,254
#4	#2 AND #3 AND #4	2,227
#5	'randomized controlled trial' OR 'clinical trials' OR rct OR 'randomized-controlled' OR randomized OR trial OR 'controlled clinical trials' OR 'random allocation' OR 'multicenter studies' OR 'control groups' OR 'evaluation studies'	2,538,237
#6	#5 AND #4	460
	Database Name: Cochrane Library (CENTRAL) **Date Run: 17/04/2020 16:10:06**	
#1	#1 MeSH descriptor: [Hypoxia-Ischemia, Brain] explode all trees	212
#2	Hypoxic ischemic encephalopathy' OR 'Neonatal hypoxia-ischaemia' OR 'neonatal hypoxia-ischemia Asphyxia' OR 'hypoxic-ischaemic encephalopathy' OR HI OR HIE OR 'perinatal hypoxia-ischemia' OR Encephalopathy OR 'neonatal asphyxia' OR 'perinatal hypoxic-ischemic brain injury' OR 'cerebral asphyctic events' OR asphyctic OR 'Hypoxia-Ischemia, Brain' OR hypoxia OR 'hypoxic' OR 'asphyxia' OR 'hypoxic-ischemic encephalopathy' OR 'perinatal asphyxia' OR 'birth asphyxia' OR 'ischemia' OR 'Brain Ischaemia' OR 'Hypoxia-Ischemia' OR Brain Ischemia OR 'Hypoxia Asphyxia' OR 'Neonatal Hypoxic-ischemic encephalopathy'	40156
#3	#1 OR #2	40156
#4	MeSH descriptor: [Melatonin] explode all trees	1190
#5	Melatonin OR "N-acetyl-5-methoxytryptamine" OR ramelteon OR indolamine	2986
#6	#4 OR #5	2986
#7	MeSH descriptor: [Infant, Newborn] explode all trees	15916
#8	MeSH descriptor: [Infant, Premature] explode all trees	3752
#9	Neonates OR Newborn OR infants OR 'late preterm' OR term OR preterm OR newborns OR infant OR neonate	224256

#10	#7 OR #8 OR #9	224256
#11	#3 AND #6 AND #10 ----------	16
	CINAHL search dated April 17, 2020	
S1	(MH "Hypoxia-Ischemia, Brain, Neonatal")	240
S2	Hypoxic ischemic encephalopathy' OR 'Neonatal hypoxia-ischaemia' OR 'neonatal hypoxia-ischemia Asphyxia' OR 'hypoxic-ischaemic encephalopathy' OR HI OR HIE OR 'perinatal hypoxia-ischemia' OR Encephalopathy OR 'neonatal asphyxia' OR 'perinatal hypoxic-ischemic brain injury' OR 'cerebral asphyctic events' OR asphyctic OR 'Hypoxia-Ischemia, Brain' OR hypoxia OR 'hypoxic' OR 'asphyxia' OR 'hypoxic-ischemic encephalopathy' OR 'perinatal asphyxia' OR 'birth asphyxia' OR 'ischemia' OR 'Brain Ischaemia' OR 'Hypoxia-Ischemia' OR Brain Ischemia OR 'Hypoxia Asphyxia' OR 'Neonatal Hypoxic-ischemic encephalopathy'	78,890
S3	S1 OR S2	78,890
S4	(MH "Melatonin")	2,686
S5	Melatonin OR "N-acetyl-5-methoxytryptamine" OR ramelteon OR indolamine	3,683
S6	S4 OR S5	3,683
S7	(MH "Infant, Newborn+")	140,288
S8	(MH "Infant, Premature")	23,095
S9	Neonates OR Newborn OR infants OR 'late preterm' OR term OR preterm OR newborns OR infant OR neonate	665,438
S10	S7 OR S8 OR S9	665,438
S11	(S7 OR S8 OR S9) AND (S3 AND S6 AND S10)	29

LILAC: Run on 17 April 2020

Database : **LILACS**

Search on : **Hypoxic ischemic encephalopathy' OR 'Neonatal hypoxia-ischaemia' OR 'neonatal hypoxia-ischemia Asphyxia' OR 'hypoxic-ischaemic encephalopathy' OR HI OR HIE OR 'perinatal hypoxia-ischemia' OR Encephalopathy OR 'neonatal asphyxia' OR 'perinatal hypoxic-ischemic brain injury' OR 'cerebral asphyctic events' OR asphyctic OR 'Hypoxia-Ischemia, Brain' OR hypoxia OR 'hypoxic' OR 'asphyxia' OR 'hypoxic-ischemic encephalopathy' OR 'perinatal asphyxia' OR 'birth asphyxia' OR 'ischemia' OR 'Brain Ischaemia' OR 'Hypoxia-Ischemia' OR Brain Ischemia OR 'Hypoxia Asphyxia' OR 'Neonatal Hypoxic-ischemic encephalopathy' [Words] and Melatonin OR "N-acetyl-5-methoxytryptamine" OR ramelteon OR indolamine [Words]**

References found : **11** [refine]

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YOUR SELECTION | >> SEND RESULT | NEW SEARCH | CONFIG | PAGE BOTTOM

Database : **LILACS**

Search on : **Hypoxic ischemic encephalopathy' OR 'Neonatal hypoxia-ischaemia' OR 'neonatal hypoxia-ischemia Asphyxia' OR 'hypoxic-ischaemic encephalopathy' OR HI OR HIE OR 'perinatal hypoxia-ischemia' OR Encephalopathy OR 'neonatal asphyxia' OR 'perinatal hypoxic-ischemic brain injury' OR 'cerebral asphyctic events' OR asphyctic OR 'Hypoxia-Ischemia, Brain' OR hypoxia OR 'hypoxic' OR 'asphyxia' OR 'hypoxic-ischemic encephalopathy' OR 'perinatal asphyxia' OR 'birth asphyxia' OR 'ischemia' OR 'Brain Ischaemia' OR 'Hypoxia-Ischemia' OR Brain Ischemia OR 'Hypoxia Asphyxia' OR 'Neonatal Hypoxic-ischemic encephalopathy' [Words] and Melatonin OR "N-acetyl-5-methoxytryptamine" OR ramelteon OR indolamine [Words]**

References found : **11** [refine]

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page 1 of 2 *go to page* **1** 2