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Melatonin as a treatment after Traumatic Brain Injury: A systematic review and meta-analysis of the pre-clinical and clinical literature

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Melatonin as a treatment after Traumatic Brain Injury: A systematic review and meta-analysis of the pre-clinical and clinical literature

Karen M. Barlow, MD; Michael J. Esser, PhD; Myra Veidt; Roslyn Boyd, PhD

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Abstract

Traumatic brain injury is common and yet effective treatments of the secondary brain injury are scarce. Melatonin is a potent, non-selective neuroprotective and anti-inflammatory agent that is showing promising results in neonatal brain injury. The aim of this study was to systematically evaluate the pre-clinical and clinical literature for the effectiveness of Melatonin to improve outcome after TBI. Using the systematic review protocol for animal intervention studies (SYRCLE) and Cochrane methodology for clinical studies, a search of English articles was performed. Eligible studies were identified and data was extracted. Quality assessment was performed using the SYRCLE risk of bias tool. Meta-analyses were performed using standardized mean differences (SMD). Seventeen studies (15 pre-clinical, 2 clinical) met inclusion criteria. There was heterogeneity in the studies, and all had moderate-to-low risk of bias. Meta-analysis of pre-clinical data revealed an overall positive effect on neurobehavioural outcome with SMD of 1.51 (95% CIs: 1.06-1.96). Melatonin treatment had a favorable effect on the neurological status, by a SMD of 1.35 (95% CI: 0.83-1.88) and cognition by a SMD of 1.16 (95% CIs: 0.4-1.92). Melatonin decreased the size of the contusion by a SMD of 2.22 (95% CI: 0.84-3.59) and cerebral oedema by SMD of 1.91 (95% CI: 1.08-2.74). Only two clinical studies were identified. They were of low quality, used for symptom management, and were of uncertain significance. In conclusion, there is evidence that Melatonin treatment after TBI significantly improves both behavioural outcomes and pathological outcomes, but significant research gaps exist especially in clinical populations.

Key Words: Traumatic Brain Injury, Melatonin, Systematic Review

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Introduction

Traumatic brain injury is one of the commonest causes of neurological morbidity and death worldwide [1]. Recent estimations suggests an incidence of 790/100,000 person years [2]. Despite being common, evidence supporting its management and specific treatments are lacking [3]. After the acute injury, a torrent of complex and varied pathophysiological processes ensue that unfortunately result in further significant secondary brain injury but that also potentially offers a therapeutic window [4]. Part of the problem in making treatment advances is that the injuries themselves are diverse, and they occur in markedly varied biopsychosocial settings, which influences outcome. As many treatments that have focused on a specific pathway or symptom have failed to show efficacy in human studies, it becomes attractive to consider a non-selective agent as a therapeutic candidate [5, 6].

Melatonin (MEL) could be a promising neuroprotective agent in traumatic brain injury (TBI). Although MEL's role in the chrono-regulation of major physiological processes (e.g., the sleep wake cycle) is well accepted [7, 8], more recently its therapeutic potential is being explored in acquired brain injury, most notably neonatal hypoxic-ischemic encephalopathy [9-11]. MEL has pluripotent antioxidant and anti-inflammatory properties [12-15], that are both receptor-mediated (at physiological levels) and non-receptor mediated (especially at supra-physiological levels) [16-19]. Further its lipophilic properties allow it to cross cell membranes easily and reach subcellular compartments [20]. The latter is a useful property considering that TBI results in widespread cellular process disruption such as metabolic cascades, indiscriminant neurotransmitter release, oxidative stress, and mitochondrial dysfunction. Indeed a recent Neurotrauma Pharmacology working group identified a need for pharmacotherapies that promote neurorepair, neuroregeneration, and neuroprotection [6].

Melatonin affords neuroprotection through a wide variety of mechanisms [18] including; acting as a direct free radical scavenger and anti-oxidant[21] through reduction in oxidative stress by decreasing oxidative/nitrosative species and by increasing antioxidant enzymes[22-25]. MEL also improves mitochondrial function by increasing electron transport and the function of complexes I and IV and by decreasing direct mitochondrial oxidative damage [26-

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[28]. As an indirect and direct consequence of these actions, MEL has also been shown to inhibit programmed cell death (apoptosis), is also inhibited by MEL [29-31].

In addition to protection from toxic metabolic intermediaries, MEL has also been shown to modulate neurotransmitter effects in TBI and other neurological conditions. Excessive release of the excitatory neurotransmitter glutamate occurs immediately after TBI [32]. MEL has the potential to "balance" this due to its action at inhibitory gamma-aminobutyric acid (GABA) receptors, especially $GABA_A$ receptors [33-36]. It has been also shown to decrease the neurotoxicity associated with beta-amyloid which accumulates in several neurodegenerative diseases including chronic traumatic encephalopathy (CTE) [37]. Neuroinflammation is also thought to play a role in TBI and CTE [38]. Although inflammation and glial cell activation after TBI can be beneficial, if excessive it can lead to significant damage and impaired function. Melatonin. MEL is a potent anti-inflammatory agent [13, 39, 40]. It achieves this partly through cytokine signaling and also indirectly by decreasing the inflammatory mediators nitric oxide and maldondialdehye production [41].

Not only is MEL attractive due to its neuroprotective properties, but it also offers therapeutic potential for many of the common post-TBI symptoms such as sleep disruption, pain, mood disturbance and increased anxiety [42-47]. Melatonin can help the initiation of sleep via its action on Melatonin receptors[48] and can also decrease pain both at the tissue level and by modulating the opioid and GABAergic systems [49, 50]. Melatonin may be useful in migraine [51, 52] and has efficacy in disorders of chronic pain and anxiety [53, 54]. Importantly, Melatonin has an excellent side effect profile with good tolerability in high does and even in children [55-57].

In summary, Melatonin may offer safe non-selective neuroprotection and symptomatic treatment following TBI. The aim of this study was determine the effect of treatment with Melatonin (or other melatonergic agent) on the outcome (anatomical, cognitive, physical, or behavioural) after TBI compared to control or usual care in either humans or animals.

Methods:

The following databases were comprehensively searched between July and December 2017 by investigator KMB: The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), PubMed (1951- December 2017), CINAHL (1982- December 2017), PsycINFO (1966- December 2017), MEDLINE (OVID) (1948 to Dec 2017), Embase (1988- December 2017) and the National Institute of Health Clinical Trials Database, 2017. The following search strategy was used using the MeSH headings or Keywords: 1) Human OR Animal AND Brain injuries AND Melatonin OR N-acetyl-5-methoxytryptamine OR melatonergic agent AND child development OR infant development OR cognition OR intellectual disability OR developmental disabilities OR psychomotor performance OR psychomotor disorders OR sleep OR psychological OR behaviour OR language OR outcome OR mortality OR morbidity OR brain damage, chronic. Studies were included if they were reported in English or if translations could be obtained from the author.

Selection criteria:

Studies had to meet the following selection criteria for inclusion: (1) randomized controlled trial (RCT) or comparative trials using a control group or case series (greater than 10 participants) satisfying inclusion criteria for types of participants, interventions and outcomes. (2) The study population included adults and children (ages 0 to 19 years, including neonates) and animals with a traumatic brain injury. (3) Treatment with Melatonin OR N-acetyl-5-methoxytryptamine OR melatonin analog or melatonergic agent. The intervention group had to have been compared to a group receiving sham, placebo or other non-experimental control in the animal. In the human, in order to be inclusive, the same criteria as for the animal were used and also included case series. (4) Treatment could begin either before the injury or at any time point post injury and could be provided in the lab, at home, or in hospital. (5) Any validated outcome measure assessing anatomical, physical, cognitive and/or behavioural outcome. A wide variety of measures tend to be employed across studies and so we did not require that each one has been validated in the TBI population as this was anticipated to limit the number of studies that could be included. Functional outcome assessed by objective, validated, reliable scales

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were included. Studies using global outcome scores such as the Glasgow Outcome Score (GOS), mortality and morbidity rates were also included; and (7) full text available within a peer-reviewed journal, published in English. Articles that reported on the same sample were treated as a single study.

Two of the authors independently (KMB, MV) assessed the eligibility of studies for inclusion in the review by firstly reviewing articles by title and abstract to exclude those not meeting inclusion criteria. Articles that appeared to meet the inclusion criteria were further evaluated by the full text. Consensus for article inclusion was reached by discussion between the authors (KMB, MV, ME).

Data Extraction

Details about the study design and population demographics were extracted from the included studies (Table 1). The theoretical structure, content and dosage of the intervention programs were tabulated (Table 2). Relevant data from the studies were extracted by the first author, including outcome measures (Table 3).

Data Synthesis

Quantitative analysis was conducted using Review Manager (RevMan) version 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Treatment effects were first calculated separately for each study outcome. Treatment effects for pooled data were then calculated across trials, where possible, for specific outcomes and domains. For all analyses, a random effect, inverse variance model was used to calculate standardized mean differences (SMD) and 95% confidence intervals (CI). The effect of heterogeneity (I^2) was used to measure the degree of inconsistency across pooled studies due to variability rather than chance, with larger values indicative of high heterogeneity.

Data Quality

Two independent reviewers (KMB and MV) assessed the risk of bias and the methodological quality using the SYstematic Review Centre for Laboratory animal

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Experimentation (SYRCLE) Risk of Bias tool [58] for animal studies and Downs and Black Criteria [59] for human studies (Tables 2 and 4). The SYRCLE scale has demonstrated reliability and consists of 10 items each with a score of "high", "unclear" or "low" risk of bias. Where no mention of treatment randomization was made then the study was awarded a "high" risk of bias, but randomization without mention of the process was given a score of "unclear". A "low" risk of bias was awarded when baseline characteristics of weight, sex, age and strain of the animals were provided. When animals were sacrificed immediately without returning to housing then this category was ranked as "low" risk. If outcome was objectively assessed using computerized methods only then this category was awarded "low" risk of bias. Otherwise, blinding of outcome assessors was categorized as "high" risk when no specific mention of blinding was made. Selective outcome reporting was not scored as most animal protocols are not yet published/registered. The quality of human studies was evaluated using the Downs and Black quality assessment tool, which assigns an individual score calculated out of 29 total points for each study. Discrepancies were resolved by discussion. The protocol for this systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number PROSPERO 2017 CRD4201707302).

Results

The selection process for included studies is shown in Figure 1. After removing duplicates, 213 studies were screened by title and abstract review. Twenty-two studies were identified for detailed review and a further 3 studies were identified from references lists of review articles. Fifteen preclinical studies with unique data examining the neuroprotective effects of MEL and two clinical studies examining it's use for symptom management after TBI were included, see Tables 1 and 2. Sample sizes were small in all studies, 4 to 16 in experimental preclinical groups, and 7 and 12 in clinical studies. 16 studies were controlled trials; one study was a retrospective controlled cohort study.

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Pre-clinical studies

TBI Model and Severity of Injury

A variety of animals were used: 9 rat, 5 mice and 1 rabbit, see Table 1. Most were young adults, although two models were juvenile rat models, postnatal day 7 and 30 [70, 72]. In keeping with the influence of sex on outcome following animal and human TBI, adult animals were all male, except for the rabbit model [61]. Several different mechanistic models of TBI were employed; more focal injuries were obtained using closed head injury (CHI), controlled cortical impact (CCI) or fluid percussion models (FPI)[30, 40, 60, 61, 64, 67-71, 74, 75], and diffuse injuries were obtained either by the Marmarou method [63, 65] or acceleration/deceleration model [72]. The resultant injuries were moderate to severe in all cases except for one mild TBI model [72]. Although Bayir et al. report their TBI model as mild the injuries on MRI would suggest moderate/severe TBI [61].

Interventions:

The range of MEL doses is shown in Table 2 and ranged from 0.625mg/kg to 200mg/kg, although the most frequent dose was 5mg/kg. The intervention was given once in 6 studies[60, 61, 69, 70, 74, 76] and in 9 studies the dose was repeated up to 14 times[72]. The total MEL dose was between 0.625 to 300mg/kg. The control intervention was the agent or vehicle used to dissolve and administer the MEL (usually ethanol and saline). All interventions were given by intraperitoneal injection (IP) except orally in one study [72]. The interventions were commenced 20 minutes before the injury [69], within 5 minutes of the injury [30, 60, 64, 65, 67-71, 75], at 1 hour [63, 74], or 4 hours post-injury [61]. No adverse events due to the interventions were reported in the pre-clinical studies.

Qualitative analysis

None of the pre-clinical studies had published protocols nor were registered with CAMARADES. Therefore, the selective outcome reporting item on the SYRCLE tool was not scored. There was insufficient information reported for many (41%) of the remaining 9 questions which were scored as “unclear”. Overall, all studies had significant risks of bias, see Table 4. The average SYRCLE score was 15.3 (95% CI: 14.4, 16.1). Although 4 studies[60, 65, 68, 69] scored above the 95% CI they were not sufficiently remarkable as to be excluded from any analyses. Nine studies reported any randomization, although details were not

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given. Only 30% reported any blinding, either of investigators, animal handlers or outcome assessors, see Figure 2. None of the studies reported sample size calculations. Indeed, nine studies (60%) had sample sizes of 6 per group or less.

Outcome:

A variety of outcome measures were used, see Table 3. The commonest were i) brain water content as a marker for cerebral edema (8 studies) reported between 8 and 72 hours post injury; ii) lesion/contusion volume (7 studies) measured between 8 hours and 14 days post-injury; iii) Neurological Symptom Scores (NSS, or variant; 5 studies) and iv) the Morris Water Maze test (MWM) (escape latency; used in 4 studies). The NSS when measured was done repeatedly between 1 hour and 7 days (see table 3). Similarly MWM test was measured repeatedly between day 1 and 4 post-injury except in one study[68]. These measures were used in meta-analyses of the preclinical studies. All motor outcomes differed in each of the 4 studies, see Table 3. Some motor outcomes required more balance and coordination (e.g. Rotarod test) than others (e.g. Grip test).

Stratified meta-analyses

There was a significant effect of treatment with MEL on both pathological outcome measures, Figures 2, and behavioural measures, Figures 3.

Pathological outcomes: Melatonin decreased the size of the contusion by a SMD of 2.22 (95% CI: 0.84, 3.59; 6 studies, 7 comparisons). The effect size was large being greater than 3.0 for 4 of the 6 studies with the largest being 4.5[40]. MEL decreased cerebral oedema by SMD of 1.91 (95% CI: 1.08, 2.74; 6 studies, 9 comparisons). Six of nine studies reported significantly large effect sizes ranging from 1.5 to 3.9. There was significant heterogeneity between the studies (I^2: 84%). However, this finding was supported by two studies not included in the meta-analysis. One reported a decrease in intracranial pressure (ICP) in association with MEL treatment [63]. In another study, MEL had a similar effect on brain protrusion (a marker of increased ICP) as 20% Mannitol [61] - a first-tier therapy for increased ICP following TBI [77].

Behavioural outcomes: Melatonin treatment had a favorable effect on the neurological status, see Figure 3 by a SMD of 1.35 (95% CI: 0.83, 1.88; 5 studies 8 comparisons). The

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outcome closest to 24 hours post-injury was compared in the meta-analysis. Five of the 8 experiments reported significantly large effect sizes associated with MEL treatment, ranging from 1.0 to 3.5. Meta-analysis demonstrated that overall MEL improved the performance on a memory-based cognitive task by a SMD of 1.16 (95% CIs: 0.4, 1.92). There was a large effect size ranging from 1.1 to 2.4. Only one study examined the effect of MEL on mood and anxiety [72]. This was done between day 7 and 13 post injury and showed no effect of treatment. Motor outcomes were also improved by MEL (SMD 0.93; 95% CI:0.69, 1.93).

Overall effect

When all studies and comparisons were combined, the overall outcome was improved by a SMD of 1.51 (95% CI, 1.06, 1.96; 15 studies, 20 comparisons), see Figure 4. One outcome measure from each study was included in the following priority: neurological status, cognitive function, contusion size and cerebral oedema. As expected the heterogeneity was moderately high (I^2 58%). Nine comparisons had effect sizes greater than 1.5.

Dose, timing of intervention, and frequency

Four studies examined the effect of differing doses on outcome [63, 69, 74, 75]. The dose, timing and frequency of interventions varied greatly making it difficult to draw conclusions. The effects of frequency of dose regimes and timing of interventions were analyzed in *ad hoc* subgroup analyses of the overall outcome. Interventions were considered to be “early” if given before 30 minutes and late if given after 60 minutes, see Figure 5. There was no significant effect of single versus multiple dosing (Chi^2 2.26, df 1; p=0.13) nor “early” or “late” treatment subgroups (Chi^2 0.2, df 1; p=0.66), see Figure 6.

Clinical Studies

Two clinical studies were identified. There was no placebo controlled study. Kemp et al. examined the effectiveness of MEL in seven male adults with sleep disturbance and was of good methodological quality except for being significantly underpowered [78]. The TBI ranged from mild to severe and occurred 36 months (range: 9 to 73) previously. A double blind randomized crossover study was performed using 5mg of oral MEL in comparison to 25 mg Amitriptyline for 4 weeks [78]. There was no effect of MEL treatment on sleep or

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neuropsychological parameters compared to the active comparator, Amitriptyline. No adverse events were reported.

Kuczynski et al. reported an open-label retrospective cohort study of children (mean age 14 years, SD 3.1) with postconcussion syndrome and post traumatic headaches 8 months following mild TBI[46]. Although a beneficial effect of MEL was reported: 75% (95% CI: 49, 88) had greater than 50% improvement in the number of headaches, the study was uncontrolled. The effect on sleep was not reported. No adverse events were reported. Caution should be observed when drawing any conclusion from this study due to its low methodological quality.

DISCUSSION

The goal of this review was to systematically evaluate the literature for the efficacy of Melatonin as a potential treatment to improve outcome after TBI. Pre-clinical intervention studies, although often focused on a biological construct, ideally have either a pathological or behavioural outcome consistent with clinical realities in order to add validity and allow clinical correlation. By necessity pre-clinical studies often have small sample sizes. A systematic review combined with meta-analysis allows the data to be methodologically and objectively assessed. This is the first systematic review of the evidence supporting the use of MEL in animal models and humans with TBI. Based on the results of our meta-analysis in pre-clinical studies, there is potential for treatment with MEL to improve functional outcome.

Melatonin significantly improved neurobehavioural outcome in neurological, cognitive, and motor domains, as well as histopathological domains (contusion size and cerebral oedema). There was an overall positive standardized mean difference of 1.51 (95% CI, 1.06, 1.96). This is similar to its effect in a systematic review of preclinical stroke models [79] and meta-analysis of MEL as a treatment for pain in adults [80]. Although the results of this meta-analysis are strengthened by the effect seen across multiple species (mouse, rat, and rabbit), it is significantly weakened by the significant methodological differences, especially dose and timing of treatments.

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After injury, Melatonin was administered within minutes or up to several hours later and was used as a single treatment in some and repeated treatment in other studies. Timing theoretically could target different mechanisms e.g., early administration affecting glutamate toxicity and free radical formation; and later doses targeting neuroinflammation [13, 21]. As secondary brain injury is a rapidly progressive process, especially in the first few days, timing of drug administration is likely to be important [4]. In humans, MEL achieves maximum concentrations around 45 minutes when given orally (2 hours if given intravenously), except when slow-release preparations are used (2 hours). And its half-life is around 2 hours [57]. Here, although earlier treatment was found to be beneficial in one larger study [69], we did not find an effect of single versus multiple dosing regimens nor of early versus late initiation of treatment in subgroup meta-regression analysis. However, the variability of drug dosage (total dose: 2.5mg to 300mg) make these assessments less reliable. This is especially relevant as larger doses of MEL result in greater serum concentrations, at which supraphysiological non-receptor mediated effects occur (e.g. direct free radical scavenging, enhancement of mitochondrial function) [27]. For example, two studies found MEL 5mg/kg was more effective than 1mg/kg or 2.5mg/kg [69, 74].

Most pre-clinical studies had moderate or unclear risks of bias. A key factor in this was the lack of reporting detail to allow satisfactory experimental evaluation. Further, many investigators failed to either randomize or blind assessors and animal carers to the treatment condition. No studies provided sample size estimation or published protocols. This emphasizes the need for more rigor in applying reporting standards and for the publishing of experimental protocols.

In clinical studies there was a lack of well-designed and adequately powered trials and the two studies identified in the review evaluated the use of MEL in the chronic phase of TBI recovery for specific symptoms, headache [46] and sleep [78]. These were of low quality. The randomized controlled crossover trial was significantly underpowered and unlikely to detect difference from an active comparator (Amitriptyline) [78]. The other clinical study was retrospective [46]. Overall, although MEL was well tolerated, there was a lack of data to support the use of MEL as a neuroprotective agent or for specific symptom management in clinical populations.

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This current study has many strengths. Firstly, it is a systematic review of the current evidence and followed a published protocol method to ensure a diligent and rigorous review process. By conducting a meta-analysis, studies were combined to increase overall sample size and statistical precision. Finally, included studies had functional neurological outcomes across the many domains of neurological impairment seen after TBI and so clinical inferences can be easily made.

Although we attempted to be comprehensive, this review may have failed to identify studies and also be subject to publication bias. We did not include unpublished data and this may have skewed our results. All the studies in this review had small sample sizes and when combined with a relative paucity of studies the meta-analysis is limited by a small dataset. This systematic review has not investigated dosage or length of treatment beyond the first few days. It was not possible to examine the effects of MEL in specific TBI populations such as youth and the elderly who may have different response to the treatment. Nor were there sufficient studies to allow the evaluation of its use in different TBI pathologies e.g. diffuse versus focal injury.

Conclusions

There is evidence from pre-clinical studies that Melatonin treatment after TBI significantly improves both behavioural outcomes and pathological outcomes, but significant research gaps exist. There is insufficient clinical data to support routine use following TBI but further clinical research is warranted to evaluate whether Melatonin is a viable and safe adjunctive treatment to improve outcome after traumatic brain injury.

Author Disclosure Statement

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Table 1: TBI model, study design and quality assessment of included studies

Study	TBI Model	Animal	Age	Sex	Weight	Design	Treated (n)	Control (n)	QA score
Ates 2006(60)	CCI	Rat [1]	Adult	M	200–250g	RCT	12	12	17
Bayir 2008(61)	CHI	Rabbit [2]	Adult	MF (7,5)	2000-2500g	CT	6	6	16
Beni 2004 (62)	CHI mod/severe TBI	Mouse [3]	Adult	M	30-42g	CT	10 (7 path)	23 (7 path)	16
Campolo 2013(40)	CCI	Mouse [4]	Adult	M	25–30g	RCT	10	10	15
Dehghan 2013(63)	Marmarou severe TBI	Rat [5]	Adult	M	250-300g	RCT	7	7	14
Ding 2014(64)	Weight drop	Mouse [6]	Adult	M	28–32g	CT	10, (6 path)	10, (6 path)	15
Ding 2015(65)	Marmarou	Mouse [6]	Adult	M	28–32g	CT	5	5	17

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Kabadi 2010(66)	Fluid percussion	Rat[7]	Adult	M	300–350g	CT	7-8	9	16
Kelso 2011(67)	CCI	Rat[7]	Adult	M	225–275g	RCT	4	4	16
Lin 2016(68)	CCI	Rat[7]	Adult	M	220–250g	RCT	10 (5 path)	10 (5 path)	17
Mesenge 1998(69)	CHI Weight drop	Mouse [8]	Adult	M	25-30g	RCT	14-16	16	13
Ozdemir 2005(70)	CHI Weight drop	Rat [1]	Juvenile	MF	Age: P7	CT	7	7	17
Sarrafzadeh 2000(71)	CCI moderate TBI	Rat[7]	Adult	M	Mean: 300g	RCT	7	7-8	13
Wu 2016(30)	CCI	Rat[7]	Adult	M	300–330g	RCT	12	12	13
Yamakawa 2017(72)	mTBI accel/decal	Rat[7]	Juvenile	MF	Age: P30	RCT	5	5	15
Human studies		Setting	Population		Mean Age (years)				
Kemp	TBI severity:	Community	Adults with	M	39.4	Double-blind	7	7	19/29*

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2004(73)	mild (2), moderate (3), severe (2)	rehabilitation program	sleep problems		(range: 17-55)	crossover RCT			
Kuczynski 2013(46)	Mild TBI	Tertiary concussion clinic	Children with post-traumatic headaches	66% F	14.1 (SD 3.1)	Retrospective cohort study	12	32	11/29*

Animal species: [1]Albino Wistar rat; [2]New Zealand rabbit; [3]Sabra mouse; [4]CD1 mouse; [5]Albino N-Mary rat; [6]ICR mouse; [7]Sprague-Dawley rat; [8]Swiss mouse

TBI models: Controlled Cortical Impact (CCI); Closed Head Injury (CHI); Marmarou method (diffuse injury); Fluid percussion; Acceleration/deceleration model (Accel/decal)

Study designs: Randomized Controlled Trial (RCT); Controlled trial (CT); Pathology (path); Male (M); Female (F

Quality assessment (QA) SYRCLE risk of bias tool; *Downs and Black criteria

Journal of Neurotrauma
Zwanenburg et al. Systematic review of the Oculomotor Control after Traumatic Brain Injury: A systematic review and meta-analysis of the literature 2018
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Table 2: Details of intervention

Study	Treatment	Dose (mg/kg)	Total dose (mg/kg)	Control	Time post-injury	Route	Treated (n)	Control (n)
Ates 2006(60)	MEL	100	100	TBI alone	Immediately	IP	12	12
Bayir 2008(61)	MEL	100	100	Mannitol 20% 2gm/kg	4h	IP	6	6
Beni 2004 (62)	MEL	1	1	Vehicle (5% ethanol)	1h	IP	10	23
		5	5				23	
		10	10				8	
Campolo 2013(40)	MEL	10	20	Vehicle (1% ethanol)	1h + 6h	IP	10	10
Dehghan 2013(63)	MEL	5	20	Vehicle (ethanol)	1+ 24+ 48 +72h	IP	7	7
		20	80				7	7
Ding 2014(64)	MEL	10	50	Vehicle (5% ethanol)	Immed + 1 + 2 + 3 + 4h	IP	10	10

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Ding 2015(65)	MEL	10	50	Vehicle (5% ethanol)	Immed + 1 + 2 + 3 + 4h	IP	6	6
Kabadi 2010(66)	MEL	100	100	Vehicle (PEG)	immediately	IP	7-8	9
		200	200				7-8	
Kelso 2011(67)	MEL	5	10	Vehicle (2% ethanol)	5min +1h	IP	4	4
Lin 2016 (68)	MEL	5ml/kg	15ml/kg	Vehicle (2% ethanol)	Immed + 2 + 4h	IP	10	10
Mesenge 1998 (69)	MEL (Pilot I)	1.25	5	Vehicle (HCl)	Ia 20min pre-injury + 5min + 1+ 2h	IP	14	16
		1.25	5		Ib 5min +1+ 2+ 3h	IP	15	
	MEL (Therapeutic window II)	1.25	5	Vehicle (HCl)	IIa 5min +1+ 2+ 3h	IP	15	13
		1.25	5		IIb 30min +1+ 2+ 3h	IP	15	
		1.25	5		IIc. 1+ 2+ 3 + 4h	IP	15	
	MEL (Dose finding III)	0.625, 1.25, or 2.5	2.5, 5, or 10	Vehicle (HCl)	5min, 1+ 2+ 3h	IP	15 each dose	13
Ozdemir 2005 (70)	MEL	5	5	Vehicle (5% ethanol)	immediately	IP	7	7
Sarrafzadeh	MEL	100	300	Vehicle	Day: Immed + 1 + 2h	IP	7	7-8

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2000 (71)		100		(0.1% ethanol)	Night: Immed + 1 + 2h		7	7-8
Wu 2016 (30)	MEL	10	50	Vehicle (1% ethanol)	Immed + 1, 2, 3, and 4h	IP	12	12
Yamakawa 2017 (72)	MEL	4.5	4.5	Vehicle (ethanol)	Day 1-14	Oral	5	5
Human studies								
Kemp 2004(73)	MEL	5mg orally at night	-	AMIT 25mg	Cross over trial: 1st arm: 4 weeks, washout period: 2 weeks 2nd arm:4 weeks	Oral	7	7
Kuczynski 2013(46)	MEL	3 to 10 mg	-	AMT 10-50mg; other treatments	MEL at night for 4 weeks Or AMT at night or other treatment for 8weeks	Oral	12	AMT 18; other 14

Melatonin (MEL); Immediately (immed); Hydrogen chloride (HCl); Polyethylene glycol (PEG); Amitriptyline (AMT)

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Table 3: Details of outcome measures

Study	Outcome measure	Function	Scale and Direction	Time assessed
Contusion/Traumatic lesion size				
Ates 2006(60)	Contusion volume, %	Quantitative digital analysis of the lesion size (5mm section, % ipsilateral hemisphere)	0-100% Lower score is more favorable outcome	14 days
Beni 2004 (62)	Contusion size, %	Quantitative digital analysis of lesion, (1mm sections, % of opposite hemisphere x2)	0-100% lower is better	24h
Campolo 2013(40)	Lesion volume, mm^3	Lesion volume calculated from 2mm sections	Lower is better	24h
Kelso 2011(67)	Cortical tissue spared, mm^3	Percentage of total cortical tissue volume	0-100 Higher is better	12 days
Lin 2016(68)	Lesion volume, mm^3	Quantitative digital analysis of lesion (0.5mm sections)	Lower is better	8h
Sarrafzadeh 2000(71)	Contusion volume, mm^3	Quantitative digital analysis of lesion (0.4mm sections)	Lower is better	24h
Cerebral oedema				
Dehghan	Brain water content, %	Brain water content increases as cerebral	0-100	72h

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2013(63)		oedema increases: % water content of whole brain calculated by wet weight/dry weight method (WW/DW)	Lower is better	
Lin 2016(68)				8h
Wu 2016(30)				24h
Ding 2014(64)		% ipsilateral hemisphere, WW/DW		24h
Ding 2015(65)				24h
Kabadi 2010(66)				48h
Sarrafzadeh 2000(71)				24h
Sarrafzadeh 2000(71)	Hemispheric swelling, %	% of contralateral hemisphere; [(WWL - WWR)/WWR] X 100		24h
Neurological status				
Beni 2004 (62)	Neurological Severity Score (NSS) change	Change in NSS: Ten Behavioural and motor tasks: 1 point awarded for each failed task	0 - 10 lower = less deterioration	Change from baseline at 1, 4 and 7 days;
Ding 2014(64)	NSS	NSS total score	0-10 Lower is better	1, 24* and 72h
Ding 2015(65)		Change in NSS	0-10 Higher is better	1*, 3 and 7 days

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Abstract: Traumatic Brain Injury: A systematic review and meta-analysis of the preliminary information with the author(s) and the publication date (DOI: 10.1089/neu.2018.5752)
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Wu 2016(30)	Modified NSS	Modified NSS with motor, sensory, reflex, and balance tests	0-18 Lower is better	24h
Dehghan 2013(63)	Vetnary Coma Score (VCS)	Neurological status based on motor (1-8), visual (1-4), and respiratory responses (1-3)	3 -15 Higher is better	Baseline, 1, 24, 48 and 72h
Cognitive performance				
Kelso 2011(67)	Morris Water Maze (MWM) (s)	MWM Escape latency: time to reach platform (max 60s) x 5 trials i) Data acquisition test over 5 days and ii) retention 3 days later (distance – partially reported)	Maximum 60s Lower is better	i) Day 5-9 ii) Day 12
Lin 2016(68)	MWM (s)	Escape latency(s): i) Hidden platform ii) visible platform	Maximum 100s Lower is better	i) Day 11-15 ii) Day 16
Ozdemir 2005(70)	MWM (s)	i) Escape latency (s) and ii) Time in correct quadrant (s)	Maximum 60s 1. Lower is better 2. Higher is better	i) Days 1 to 4 ii) Day 5
Yamakawa 2017(72)	Behavioural test battery: Beam walking (BW); Open field (OF); Elevated Plus Maze(EPM); Novel Context Mismatch	BW: The beam walking task measures acute balance, coordination, and motor disturbances (s); OF: a measure of locomotion and exploratory behavior;	BW: lower is better OF: higher is better EPM: higher is better NCM: higher is	BW day 1; OF day 2; EPM day 3, NCM day 7-10 FS day 13

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	(NCM); and Force Swim (FS)	EPM: a behavioural test for anxiety; NCM: a measure of short-term working memory; FS: a measure of depressive-like behavior	better FS: lower is better	
Motor function and coordination				
Campolo 2013(40)	Rotarod test (s)	Time on Rotarod (average of 3 trials)	0 – 60 Higher is better	1 and 6h;
Lin 2016(68)	Balance beam (s)	Time on beam	Higher is better	Day 1 to 5
Mesenge 1998(69)	Grip score (s)	Length of time remains on a string (mainly motor function)	Maximum 0-30 Higher is better	24h
Other outcomes				
Dehghan 2013(63)	ICP (mmHg);	Intracranial Pressure measured over 3 days (baseline, 1, 24, 48 and 72h)	Lower is better	72h*
Bayir 2008(61)	i) MRI pathology change;	Pathologies categorized: parenchymal or extra cerebral hemorrhage, contusion, ventricular effacement; 36h MRI at 3 hours post-injury, intervention given, MRI repeated at 36 hours	Lower amounts of change is more favorable i.e. less cerebral oedema	36h

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	ii) Brain protrusion through craniotomy	Maximal extrusion point of brain tissue outside craniotomy site	Lower is better	36
Kemp 2004(73)	Sleep diary; SCOLP AMIPB HAD	Tests for change in memory and information processing speeds: i) Neuropsychological Speed and Capacity of Language-Processing Test (SCOLP); ii) Information processing test from Adult Memory and Processing Battery (AMIPB); Mood assessment: Hospital Anxiety and Depression Scale (HAD)	0-100 i) and ii) higher is better iii) lower is better	End of each treatment arm
Kuczynski 2013(46)	> 50% headache frequency	Reduction in headache frequency	Dichotomous	2 months post treatment

* reported

Neurological Severity Score (NSS)

Vetnary Coma Score (VCS)

Morris Water Maze (MWM)

Beam walking (BW)

Open field (OF)

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Elevated Plus Maze (EPM)

Novel Context Mismatch (NCM)

Force Swim (FS)

Intracranial Pressure (ICP)

Speed and Capacity of Language-Processing Test (SCOLP)

Information processing test from Adult Memory and Processing Battery (AMIPB)

Hospital Anxiety and Depression Scale (HAD)

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Table 4: Methodology quality assessment of included studies using SYRCLE risk of bias tool(58)

	Random sequence generation	Baseline Characteristics	Allocation concealment	Random housing	Blinding to allocated treatment	Random outcome assessment	Outcome assessor blinding	Incomplete outcome data	Other sources of bias	Total SYRCLE Score	Any randomization	Any blinding	Sample size
Ates 2006	2	1	2	2	3	2	3	1	1	17	Y	N	N
Bayir 2008	3	1	2	2	3	1	1	1	1	16	N	Y	N
Beni 2004	3	1	2	2	2	1	3	1	1	16	N	N	N
Campolo 2013	2	1	2	2	2	1	3	1	1	15	Y	N	N
Dehghan 2013	2	1	2	2	2	1	2	1	1	14	Y	N	N
Ding 2014	3	1	2	2	1	2	1	1	2	15	N	Y	N
Ding 2015	3	1	2	2	1	2	1	3	2	17	N	Y	N
Kabadi 2010	3	1	2	2	2	1	3	1	1	16	N	N	N

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Kelso 2011	2	1	2	2	2	1	3	1	2	16	Y	N	N
Lin 2016	2	1	2	2	2	2	3	1	2	17	Y	N	N
Mesenge 1998	2	1	2	2	2	1	1	1	1	13	Y	Y	N
Ozdemir 2005	3	1	2	1	2	3	3	1	1	17	N	N	N
Sarrafzadeh 2000	2	1	2	2	2	1	1	1	1	13	Y	N	N
Wu 2016	2	1	2	2	2	1	1	1	1	13	Y	Y	N
Yamakawa 2017	1	3	2	1	2	1	3	1	1	15	Y	N	N

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Table 5: Table demonstrating mean, standard deviation, effect sizes and 95% confidence intervals for individual pre-clinical study results

Study		Melatonin			Control						
		n	**mean**	**SD**	**n**	**mean**	**SD**	**p-value for mean diff (2-tailed T-test)**	**Bias corrected effect size (Hedges)**	**95% CI**	
Contusion/lesion size											
Ates(60)	%	12	11.7	1.2	12	16.9	1.8	**<0.001**	-3.274	-2.0	-4.5
Beni(74)		7	6.2	1.0	7	11.1	1.0	**<0.001**	-4.454	-2.5	-6.4
Campolo(40)	mm^3	10	37.0	4.7	10	56.0	3.2	**<0.001**	-4.517	-2.9	-6.2
Kelso(67)		4	84.0	8.0	4	86.0	10.0	0.765	-0.192	1.2	-1.6
Lin(68)		5	8.0	1.0	5	11.2	0.8	**0.001**	-3.190	-1.3	-5.1
Sarrafzadeh(71) (night)		8	30.5	12.8	7	41.8	13.9	0.126	-0.796	0.3	-1.8
Sarrafzadeh(71) (day)		8	35.6	6.8	8	41.8	16.0	0.334	-0.473	0.5	-1.5
Cerebral Oedema											
Dehghan(63) MEL	Brain water	7	73.1	0.8	4	75.7	0.4	**<0.001**	-3.468	-1.6	-5.4

Journal of Neurotrauma
2nd revised manuscript (clean version) (07.10.2019) (new 2.0 18.07.19)
Meta-analysis of the effect of melatonin in experimental traumatic brain injury: A systematic review
Jonathan Lee Wheaton, Jr. et al.
Journal of Neurotrauma, 2019, 36(24): 3405-3423, doi: 10.1089/neu.2018.6312
This manuscript has been peer reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

5mg/kg	content, %										
Dehghan(63) MEL 20mg/kg		7	72.9	0.7	3	75.7	0.5	**<0.001**	-3.879	-1.7	-6.1
Wu(30)		12	79.8	0.3	12	80.9	0.4	**<0.001**	-3.004	-1.8	-4.2
Lin (68)		5	78.4	1.3	5	81.8	1.6	**0.006**	-2.105	-0.6	-3.7
Ding 2014 (64)		6	80.2	1.7	6	81.9	1.6	0.104	-0.953	0.2	-2.1
Ding2015 (65)		5	80.4	0.9	5	81.9	0.9	**0.029**	-1.521	-0.1	-2.9
Kabadi (75) MEL 100mg/kg		8	79.5	0.8	5	80.5	0.8	0.060	-1.110	0.1	-2.3
Kabadi (75) MEL 200mg/kg		8	79.1	0.3	4	80.5	0.6	**<0.001**	-3.087	-1.4	-4.8
Sarrafzadeh(71)		7	80.5	0.4	7	80.7	1.1	0.696	-0.199	0.9	-1.2
Sarrafzadeh(71)	Hemispheric swelling, %	7.9	7	3.4	9.2	7	4.5	0.55	-0.300	0.75	-1.36
Neurological status											
Beni (74) MEL 1mg/kg	NSS	10	4.7	1.0	8	6.5	0.9	**0.001**	-1.889	-0.8	-3.0
Beni (74) MEL 5mg/kg		23	4.5	2.2	8	6.5	0.9	**0.019**	-0.989	-0.1	-1.8

Journal of Neurotrauma
2nd revised manuscript with changes highlighted (clean version without changes highlighted) (07-13-2018).docx, at (07-13-2018 08:43:13)
Comment after Traumatic Brain Injury: A systematic review and meta-analysis of the effectiveness of Edaravone and Edaravone plus Hypothermia
This manuscript has been reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Beni (74) MEL 10mg/kg		8	4.9	2.9	7	6.5	0.8	0.184	-0.684	0.4	-1.7
Ding (64) NSS		10	2.9	2.5	10	4.9	1.9	0.060	-0.858	0.1	-1.8
Ding (65) NSS change	ΔNSS^	5	3.2	1.3	5	1.6	1.1	0.075	-1.170	0.2	-2.5
Wu(30) NSS	mNSS	5	7.5	0.4	5	9.5	0.6	**<0.001**	-3.541	-1.6	5.5
Dehghan(63) MEL 5mg/kg	VSS^	7	13.1	0.8	3	11.5	0.9	**0.021**	1.787	0.2	3.4
Dehghan(63) MEL 20mg/kg dose		7	14.2	0.8	4	11.5	1.0	**0.001**	2.850	1.1	4.6
Cognitive function											
Memory and new learning											
Kelso(67)	MWM	4	48.4	21.2	4	45.3	34.8	0.884	-0.093	1.3	-1.5
Lin(68)		10	58.4	16.4	10	80.5	20.6	**0.016**	-1.137	-0.2	-2.1
Ozdemir 2005(70) 5mg/kg		7	38.8	1.4	4	44.9	3.4	**0.002**	-2.454	-0.9	-4.1
Ozdemir 2005(70) 20mg/kg		7	40.2	1.6	3	44.9	3.4	**0.015**	-1.935	-0.3	-3.5
Yamakawa 2017(72)	NCM^	5	33.7	8.7	5	25	8.7	0.153	0.903	2.2	1.0
Exploratory behaviour											

Journal of Neurotrauma
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nt after Traumatic Brain Injury: A systematic review and meta-analysis of the pre-clinical literature, at DOI: 10.1089/neu.2018.5912)
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Yamakawa 2017(72)		OF^	5	6132	724	5	4887	724	**0.026**	1.552	0.1	3.0
Anxiety												
Yamakawa 2017(72)		EPM^	5	38.9	9.2	5	31.2	6.5	0.163	0.876	-0.4	2.2
Depression												
Yamakawa 2017(72)		FS	5	33.8	12.2	5	24.5	7.1	0.179	0.841	0.5	-2.1
Motor function												
Yamakawa 2017(72)		BW	6	5	4.2	6.9	5	5.8	0.786	-0.160	-1.1	1.4
Campolo(40)		MR^	30.25	10	18.2	25	10	10.27	0.437	0.340	-0.5	1.2
Lin(68)		BB^	48	10	6.5	25.9	10	6.5	**<0.001**	3.256	1.9	4.6
Mesenge (69)	Ia	Grip^	18.9	14	10.9	7	8	7.9	**0.014**	1.150	0.2	2.1
	Ib		17.9	15	11.6	7	8	0.9	**0.016**	1.108	0.2	2.0
	IIa		22.8	15	10.1	13.3	5	8.7	0.077	0.928	-0.1	2.0
	IIb		15.8	15	12.4	13.3	4	7.8	0.709	0.204	-0.9	1.3
	IIc		10.5	15	13.3	-13.3	4	0.8	0.685	0.221	-0.9	1.3
	IIIa		23.3	15	8.9	14.9	5	8.5	0.081	0.913	-0.1	2.0
	IIIb		19.5	15	10.8	14.9	5	8.5	0.400	0.426	-0.6	1.4
	IIIc		12.9	15	11.6	-14.9	5	8.5	0.729	0.174	-0.8	1.2
Intracranial pressure												

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Dehghan(63) MEL 5mg	ICP	12.1	7	1.1	21.9	3	0.7	**<0.001**	-8.717	4.7	12.8
Dehghan(63) MEL 20mg		10.9	7	1.1	21.9	4	1	**<0.001**	-9.415	5.3	13.5
Bayir (61)	Brain protrusion	2	6	0.8	3.4	6	1.7	0.098	-0.972	-0.2	2.2

^Higher score = more favourable outcome

Neurological Severity Score (NSS)

Morris Water Maze (MWM)

Novel Context Mismatch (NCM)

Open field (OF)

Elevated Plus Maze (EPM)

Force Swim (FS)

Beam walking (BW)

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Motorod (MR)

Balance Beam (BB)

Intracranial Pressure (ICP)

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 (DOI: 10.1089/neu.2018.5752)
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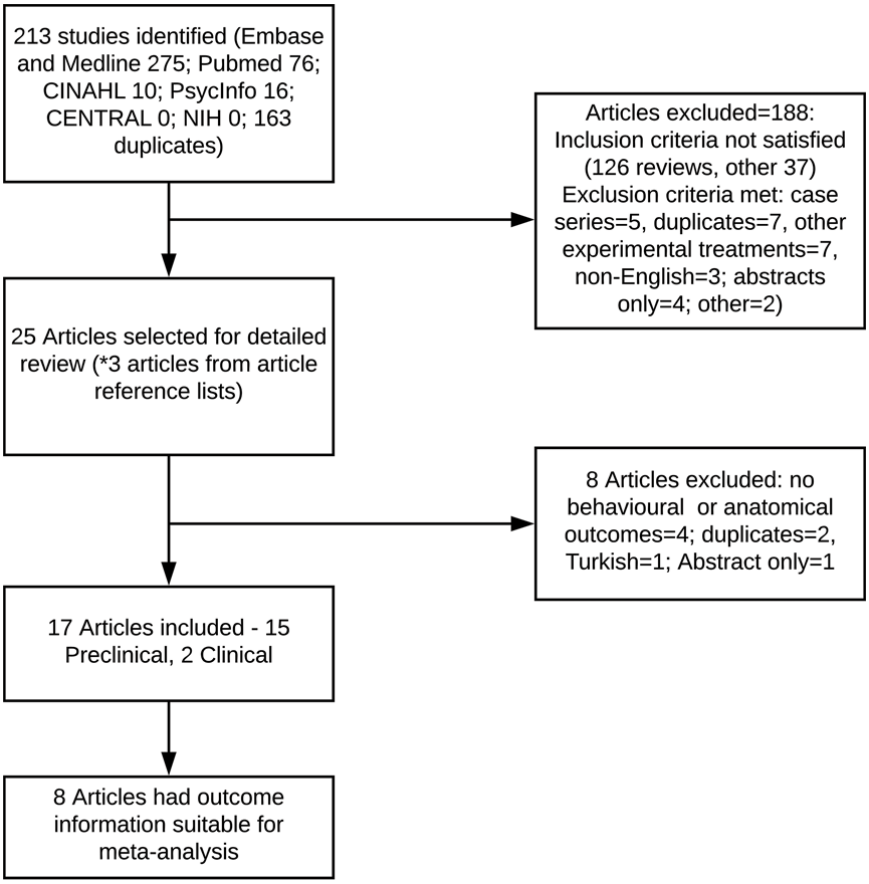

Figure 1: PRISMA diagram of included and excluded studies

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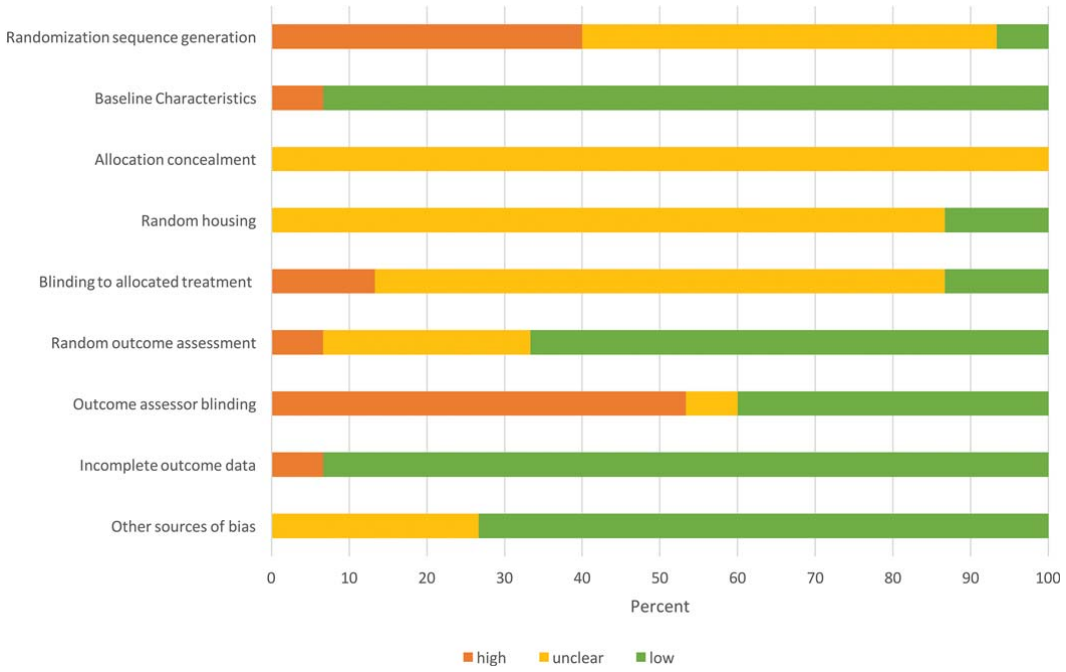

Figure 2: Assessment of bias in 15 animal studies evaluating the efficacy of Melatonin to improve TBI outcome using the SYRCLE risk of bias tool

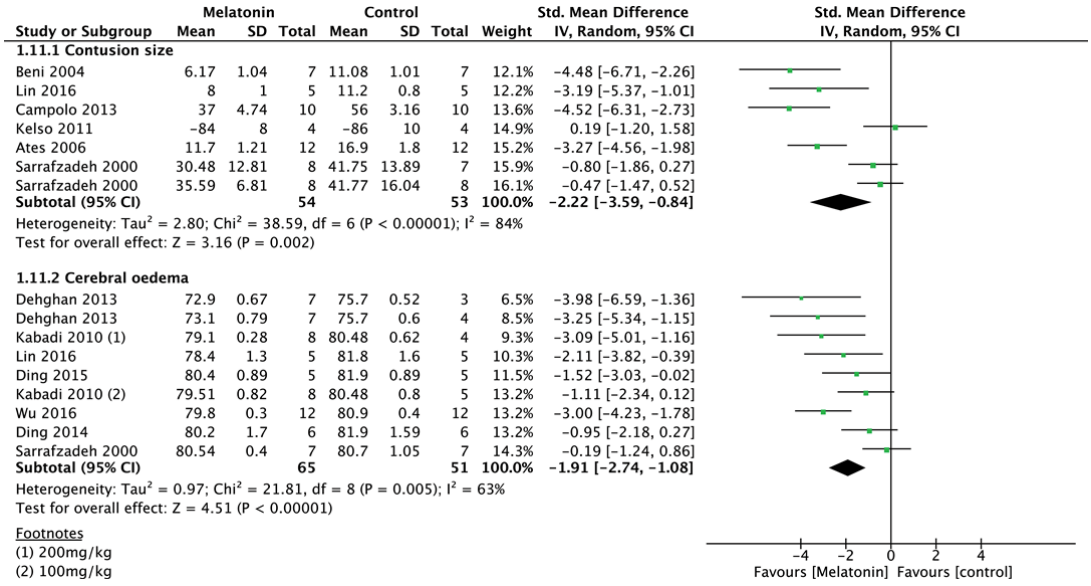

Figure 3: A Forrest Plot demonstrating the effect of Melatonin in comparison to control (vehicle) on Pathological Outcome measures in pre-clinical studies of Traumatic Brain Injury

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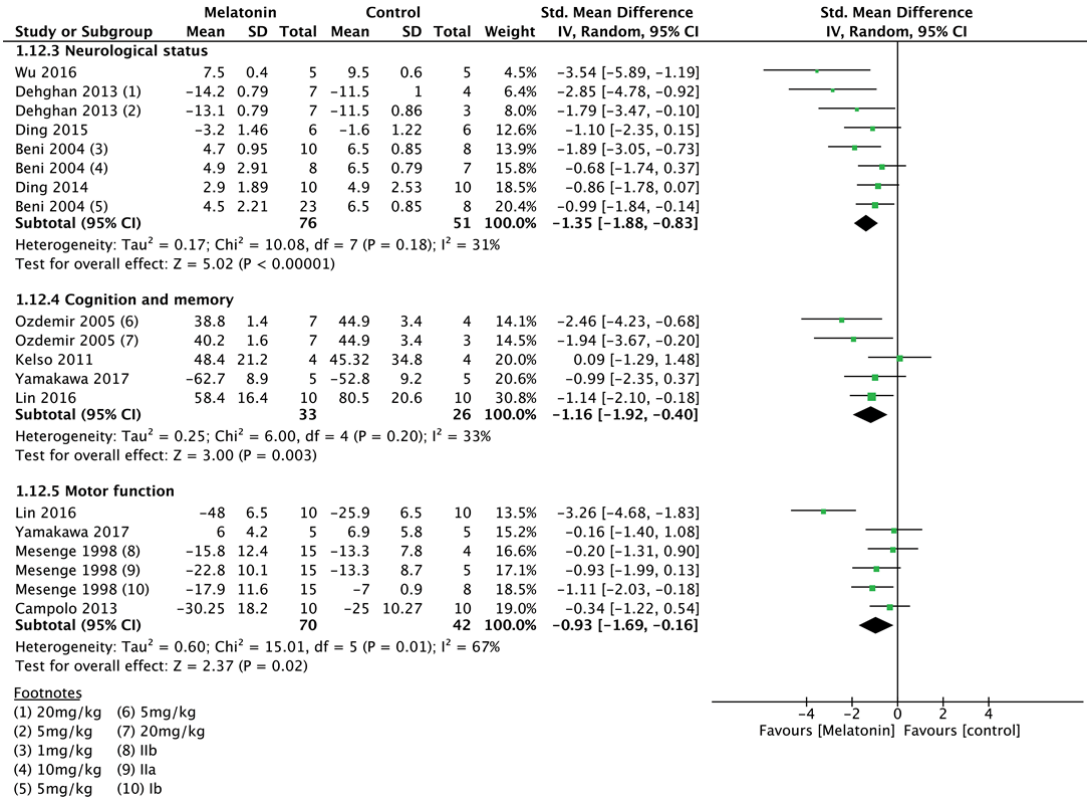

Figure 4: Forrest Plot demonstrating the effect of Melatonin in comparison to control (vehicle) on Behavioural Outcome in pre-clinical studies of Traumatic Brain Injury

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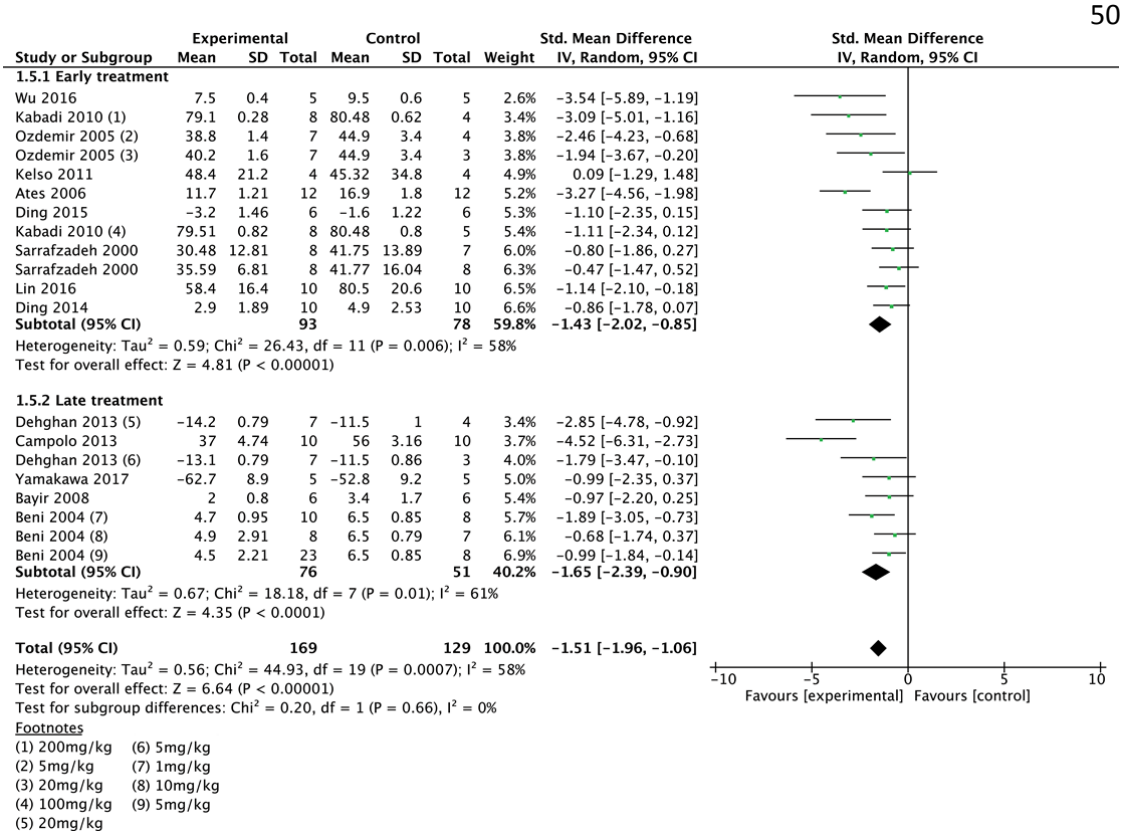

Figure 5: Subgroup Meta-analysis: efficacy of intervention versus control (vehicle) in pre-clinical studies examining single versus multiple dose and early (within 30 minutes) versus late treatment (≥1 hour) [Random effects assumed; 95% confidence intervals, CI; Effect of heterogeneity, I^2; 200mg/kg (1, 12), 5mg/kg (2, 10, 11, 13, 19, 21), 20mg /kg (3, 5, 14, 15), 100mg/kg (4, 16), 1mg/kg (6), Nighttime administration (7,17), 10mg/kg (8, 20), Daytime administration (9,18)

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