Toxicology and Applied Pharmacology 392 (2020) 114933

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/taap

Invited Review Article

Melatonin's efficacy in stroke patients; a matter of dose? A systematic review

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ARTICLE INFO

Keywords:
Melatonin
Stroke
Systematic review
Translational doses

ABSTRACT

There is a lack of effective therapies for stroke patients; its treatment is even more difficult considering the unexpected onset of the disease. In the last decade, melatonin has emerged as a promising neuroprotective agent which is able to cross the blood-brain-barrier (BBB) and with a low toxicity profile. The aim of this systematic review was to summarize and critically review clinical and pre-clinical evidence related to melatonin's effectiveness as a stroke treatment. Together with a comparative dose extrapolation with those used in the selected randomized controlled trials (RCTs), and based on these data to discuss whether the administered doses correlate with those advisable in human patients. To address this purpose, we performed a systematic review of the available literature. A total of 529 records were screened with the selecting of six full articles containing RCTs that met the inclusion/exclusion criteria. The evidence drawn from these six reports was analyzed to identify remaining gaps, treatment efficacy, and to suggest future directions. The primary outcome reported was the reduction of the oxidative response; the secondary outcome was the increase of the survival rate of the patients in the intervention groups. Calculations derived from animal studies revealed that the translational doses to humans were substantially higher than those employed in the RCTs. The findings of this systematic review revealed that there are insufficient RCTs to prove melatonin's value in stroke patients. Nevertheless, the evidence is promising, and further clinical research may support the benefits of melatonin in stroke patients, if the adequate dose is administered.

1. Introduction

Among leading worldwide causes of death, stroke is the second and the main cause of disability (Feigin et al., 2014; Guzik and Bushnell, 2017). Nevertheless, prevalence and incidence are not easy to interpret due to the lack of available global studies. More prospective studies based on population records worldwide would provide a more reliable epidemiology information. The implementation of such records in all the countries is a difficult task due to costs and time.

Concerning treatment, stroke has no effective therapy to prevent brain damage. It is accepted that the recombinant tissue plasminogen activator (tPA) reduces neuronal damage after stroke (Zivin et al., 1985; NINDS, 1995). However, a major obstacle is that it should be administered immediately, during a short therapeutic window (3,5 h). Rescuing the ischemic penumbra (adjacent tissue) includes affording excitotoxicity and disturbed calcium ion homeostasis, mitochondrial failure, oxidative and nitrosative stress, inflammation and apoptosis (Paschen, 2000; Chan, 2001; Iadecola and Alexander, 2001; Lo et al., 2005; Niizuma et al., 2010). There have been several clinically tested drugs that, unfortunately, only modulate one or two of these complex stroke related pathological events.

Melatonin (*N*-acetyl-5-methoxytryptamine) is synthesized in multiple cells and organs (Reiter et al., 2020); its blood cerebrospinal fluid levels are derived from the pineal gland (Reiter et al., 2014). Melatonin is a multifunctional molecule, mainly known for its regulatory actions of circadian rhythm (Melo et al., 2017). In most individuals, circulating

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https://doi.org/10.1016/j.taap.2020.114933
Received 4 February 2020; Received in revised form 22 February 2020; Accepted 25 February 2020
Available online 26 February 2020
0041-008X/

Table 1
Trial characteristics.

Study	Country	Sample size	Participants	Age	Dosage	Duration	Comparison	Outcome
(Fulia et al., 2001)	Italy	20	Perinatal asphyxia	newborns	10 mg/2 h	1-day single dosage	Placebo	Reduction of MDA and nitrite/nitrate levels
(Aly et al., 2015)	Egypt	45	Perinatal asphyxia	newborns	10 mg/kg	5 days	Not treated	Reduce oxidative Stress, improve survival rate and neurodevelopmental outcomes
(Dianatkhah et al., 2017)	Iran	40	Intubated stroke patients	40–69	30 mg/day	2–20 days	Not treated (No Placebo)	Length of ICU stay, and mortality
(Ahmad et al., 2018)	Pakistan	80	Perinatal asphyxia	newborns	10 mg	single dose	Not treated (No Placebo)	Survival rate
(Grima et al., 2018)	Australia	33	TBI	24–49	2 mg/day	4 weeks	Placebo	Sleep quality and efficiency
(Zhao et al., 2018)	China	60	Severe carotid stenosis	50–80	6 mg/day	6 days	Placebo and Blank	Regulates inflammation and oxidation biomarkers

Abbreviations: ICU, intensive care unit; MDA = malondialdehyde; TBI, traumatic brain injury.

melatonin levels markedly decline with natural aging (Reiter et al., 1980; Reiter et al., 1981) which likely contributes to pathophysiological changes and dysfunctions including stroke (Fiorina et al., 1996; Ritzenthaler et al., 2009; Kitkhuandee et al., 2014a, 2014b; Reiter et al., 2014).

There is a credible evidence of melatonin's therapeutic value in animal stroke models. Treatment with melatonin in stroke models (mice and rats) reduced infarct size, edema, inflammatory and apoptotic response, preserved BBB permeability and attenuated oxidative damage among others (Tables 1, 2).

When designing clinical trials, especially phase I and phase II, the dose, administration route, and timing are critical points to identify effective results. From the doses administered in animal models, an appropriate translation to humans it success is necessary to be achieved. The experimental doses should not be only extrapolated by a simple body weight conversion to a human equivalent dose (HED), the body surface area (BSA) should likewise be used as a normalization method (Reagan-Shaw et al., 2008).

The overall objectives of the current analyses was to provide a comprehensive review of the evidence for melatonin's efficacy in the treatment of stroke and to develop translational dose calculations to compare them to doses employed clinically. To date, no systematic review has been published attempting to define melatonin's effects in stroke patients.

2. Materials and methods

This review was performed according to the systematic review methodology described in PRISMA guidelines to obtain all the articles that could contain relevant RCTs and information regarding melatonin and stroke to June 20, 2019. We utilized this methodology due to its advantages, such as transparency of the methods and criteria that had been use to select and study the related reports. The following methodology was designed and approved by all authors *a priori*.

2.1. Search strategy

We develop a systematic search of Medline (https://www.ncbi.nlm.nih.gov/pubmed), Scopus (https://www.scopus.com), web of science (https://apps.webofknowledge.com) and the Cochrane library (http://www.cochranelibrary.com). This search was conducted using the following terms: (melatonin[Title/Abstract]) AND (ischemia[Title/Abstract] OR ischemic[Title/Abstract] OR Stroke[Title/Abstract] OR cerebrovascular accident[Title/Abstract]) AND (Brain[Title/Abstract] OR Cerebral[Title/Abstract]).

When available, Medical Subject Headings (MESH) terms were used. Reviews were excluded and studies were restricted to those published in English language (June 20, 2019). This search was completed with hand searches.

2.2. Study selection

Search results were exported to EndNote software v X9 (Thomson Reuters) and duplicate publications were automatically or manually removed. Thereafter, eligible articles were selected by reading the title, abstract or full-version when required. Studies were included if they were: RCTs, compared with a control group, due to the lack of RCTs numbers of participants, ages and dosage were admitted. Any disagreement regarding the selection of the trials were resolved by consensus.

2.3. Quality assessment of bias of the selected studies

To assess the methodological quality of the selected studies, the Cochrane Collaboration's table for assessing risk of bias was used (Higgins et al., 2011).

Table 2
Quality assessment of included studies based on Cochrane guidelines.

Study	Random sequence generation	Allocation concealment	Blinding of participants, Personnel and outcome assessment	Incomplete outcome data	Selective outcome reporting	Other bias	Score	Overall quality
(Fulia et al., 2001)	+	+	?	+	+	+	5	GOOD
(Aly et al., 2015)	+	?	?	+	+	+	4	GOOD
(Dianatkhah et al., 2017)	+	–	–	+	+	?	3	GOOD
(Ahmad et al., 2018)	+	+	?	+	+	+	5	GOOD
(Grima et al., 2018)	+	+	+	+	+	+	6	GOOD
(Zhao et al., 2018)	+	+	+	+	+	+	6	GOOD

Key: + low risk of bias; − High risk of bias;? Unclear risk of bias.

For each study the following criteria were assessed (Table 1):

1. Selection bias
   - o random sequence generation
   - o allocation concealment
2. Performance and detection bias
   - o blinding of participants and personnel and outcome assessment
3. Attrition bias
   - o incomplete outcome data
4. Reporting bias
   - o selective outcome reporting
5. Other biases

The domains for each study were graded in three different categories; low, high or unclear risk of bias, if the domain was considered; adequate, inadequate or insufficient information was available, respectively. The classification was developed independently by (ER and AR). After classification, the overall quality of each study was considered (Higgins et al., 2011): good (low risk > 2 item), fair (low risk = 2 item), on weak (low risk for < 2 item). The final scores were discussed by all the authors.

3. Results

3.1. Selection and identification of relevant studies

After electronic and manual literature searches of the mentioned databases, 529 studies were initially obtained. 13 duplicates that were not automatically excluded by EndNote X9 were manually removed. From the 516 records screened, 395 were irrelevant and 115 were animal studies. Finally, six studies were included for analysis. A detailed flow chart of the selection process is represented in Fig. 1.

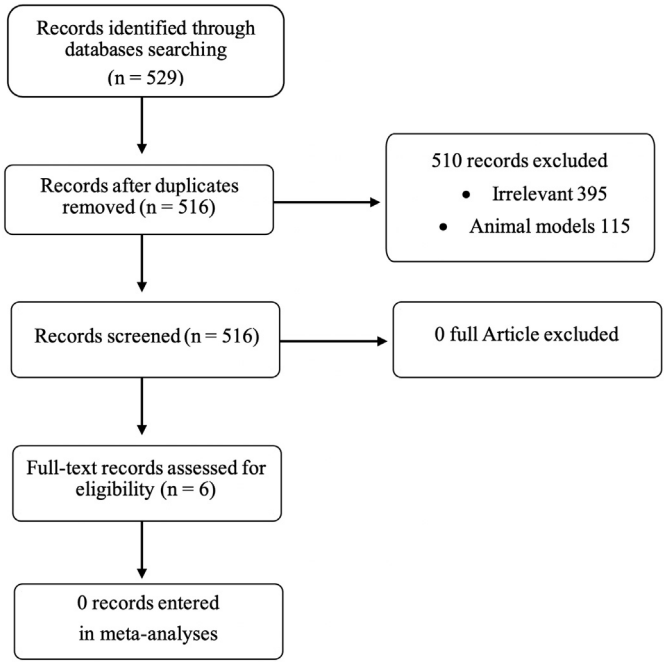

Fig. 1. PRISMA flow diagram.

3.2. Characteristics of studies

The main characteristics of the studies included are summarized in Table 1. The selected RCTs showed a wide variation, with regard to age of participants, study design, and measured outcome. Overall, 3 articles included newborns and 3 adults. The dosages ranged from 10 mg to 30 mg, administered in a single dose or during several days (from 2 to 28 days) after the diagnosis. Most of the studies included a placebo group, the exceptions were newborns where the comparison was made with a non-treated group of subjects.

A variety of the study outcomes was also conditioned by the participants age. Newborns were treated when perinatal asphyxia occurred and the main outcome measured was the improvement of the survival rate and the reduction of oxidative damage.

The summary of the risk of bias is depicted in Table 2. It was elaborated using the Cochrane collaboration tool to describe quality assessment and risk of bias on different quality domains for each study. All of them present a low risk of attrition and reporting bias. One study (Dianatkhah et al., 2017) was classified as having a high risk of selection and performance bias, despite the use a randomization method, the allocation sequence was not concealed and personnel were not blinded. When there was insufficient information for judging each domain, it was classified as unclear risk of bias. The overall quality of the RCTs was good.

3.3. Comparative doses

There are numerous preclinical studies that include melatonin treatment in stroke models. Findings of these studies frequently documented that melatonin was highly effective in improving post-ischemic damage (Ramos et al., 2017). Table 3 summarizes melatonin's effect on animal stroke models. As summarized, these studies showed that melatonin administration was routinely effective in counteracting several stroke outcomes in animals. One of the most common observations was the efficacy of melatonin in reducing infarct size (Giusti et al., 1996b; Uz et al., 1996; Sinha et al., 2001; Pei et al., 2003; Kilic et al., 2004a, 2005a, 2005b; Lee et al., 2004; Koh, 2008c; Chen et al., 2009) and, as a neuroprotectant, by improving neuronal survival and neurogenesis and reducing mortality (Giusti et al., 1996a; Sinha et al., 2001; Kilic et al., 2004b; Kilic et al., 2005a, 2005b; Hung et al., 2008; Kilic et al., 2008; Koh, 2008a, 2008b, 2008c; Koh, 2012; Juan et al., 2014; Kim and Lee, 2014; Paredes et al., 2015). Several studies additionally showed that melatonin reduced BBB hyperpermeability (Chen et al., 2006; Jang

Table 3
Comparative doses of animal studies HED extrapolation dose with clinical trials.

Animal model	Ref	Findings	Days of treatment	Melatonin daily dose (mg/kg)	Daily HED for a 70 kg adult	Clinical trials daily dose [a]
Mice	(Kilic et al., 2005a)	Reduced infarct size and the impairment of survival-promoting cell signaling (PI3K/Akt pathway)	1	4	19 mg	2,6,30 mg
	(Kilic et al., 2005b)	Reduced infarct size (30–35%). Restored Akt activity.				
	(Kilic et al., 2004a)	Reduced infarct size (30–35%). Tissue protection improving vasodilation by inhibiting ECE-1				
	(Kilic et al., 2008)	Improved neuronal survival and enhanced neurogenesis. Promoted motor and coordination deficits recovery.	29			
Mice	(Chen et al., 2006)	Reduced postischemic oxidative and nitrosative damage and preserved BBB integrity.	1	5	24 mg	
Rats	(Pei et al., 2003)	Reduced the infarct size.	1	5	48 mg	
	(Koh, 2008c)	Reduced the infarct size. Prevents cell death (*via* NOS regulation).				
	(Hung et al., 2008)	Reduced brain damage, brain edema and hemorrhagic transformation.				
	(Koh, 2008a)	Prevents cell death (mediated by the activation of Raf/MEK/ERK/p90RSK cascade).				
	(Koh, 2012)	Neuroprotection by preventing glutamate related cell damage.				
	(Pei and Cheung, 2004) (Lee et al., 2007)	Ameliorated inflammatory response.				
	(Juan et al., 2014)	Enhanced long-term neuroprotection, neuroplasticity, and brain remodeling.				
	(Lee et al., 2004)	Reduced cortical and striatal infarct sizes. Enhanced electrophysiological and neurobehavioral.				
	(Chen et al., 2009)	Reduced brain infarct size. Improves functional and electrophysiological recoveries.				
	(Koh, 2008b)	Neuroprotection mediated by Akt activation and FKHR phosphorylation (anti-apoptotic signaling pathway).				
	(Dehghan et al., 2013)	Reduced brain edema, BBB permeability and intracranial pressure, but increases veterinary coma scale after TBI	4			
Rats	(Kondoh et al., 2002) (Torii et al., 2004)	Reduced edema formation in the cerebral cortex and in the striatum.	2	6	57 mg	
Mice	(Kilic et al., 2004b)	Increased neuronal survival and decreased disseminate cell injury.	1	8	38 mg	
Mice	(Alluri et al., 2016) (Yang et al., 2015)	Protected against BBB hyperpermeability after TBI. Reduced mitochondrial oxidative damage.	1	10	48 mg	
Rats	(Giusti et al., 1996a; Giusti et al., 1996b; Uz et al., 1996; Floreani et al., 1997)	Reduced neuronal injury, behavioural and biochemical disturbances. Significantly reduced mortality. Prevented neurotoxic effects of ROS.	1	10	95 mg	
	(Paredes et al., 2015)	Ameliorated inflammatory and apoptotic response.				
	(Ozacmak et al., 2009)	Reduced oxidative stress in neurons and improved hippocampal neuronal integrity.	14			
Mice	(Kim and Lee, 2014)	Suppresses apoptosis of hippocampal neurons	3	30	143 mg	
Rats	(Jang et al., 2012)	Attenuated BBB disruption, *via* inhibition of MMP-9 activity.	3	100	955 mg	
Rats	(Deykun et al., 2011)	Improved functional outcome in animals.	1			
Rats	(Sinha et al., 2001)	Reduced oxidative damage, ischemic lesion, and improved neurological recovery.	1	40 80 160	382 mg 764 mg 1527 mg	

[a] Clinical doses used in the selected clinical trials. Abbreviations: Akt, Protein kinase B; BBB, blood brain barrier; ECE-1, endothelin converting enzyme-1; ERK, extracellular signal-regulated kinase; FKHR, forkhead transcription factor Foxo1; HED, human equivalent dose; MEK, mitogen-activated protein kinase; MMP-9, matrix metalloproteinase 9; NOS, nitric oxide synthase; p90RSK, p90 ribosomal S6 kinase; Raf, proto-oncogene serine/threonine-protein kinase; ROS, reactive oxygen species; TBI, traumatic brain injury.

Table 4
Comparative doses of newborn animal model studies to HED extrapolation dose with clinical trials.

Animal model	Ref	Findings	Days of treatment	Melatonin daily dose (mg/kg)	Daily HED for a 2,5 kg newborn	Clinical trials daily dose[a]
7-day-old rats	(Carloni et al., 2008)	Attenuated brain injury and had long-lasting benefits.	3	5 or 15	25 or 75 mg	10 mg
	(Tutunculer et al., 2005)	Protected against ROS.	1	10 or 20	50 or 100 mg	
	(Carloni et al., 2014)	Attenuated of ER stress.	1	15	75 mg	
	(Alonso-Alconada et al., 2012)	Reduced cell death, white matter demyelination, and reactive gliosis.				
	(Balduini et al., 2012)	Reduced OS, inflammation, and glial cells activation in cerebral cortex.				
	(Revuelta et al., 2016)	Reduced oxidative damage. Preserved functional integrity of the auditory pathway.				
	(Signorini et al., 2009)	Reduced oxidative damage.				
	(Villapol et al., 2011)	Did not reduce cortical infarct volume, strongly reduced inflammation and promoted myelination in the white matter.	1	20	100 mg	
	(Welin et al., 2007)	Attenuated cell death and the inflammatory response.				

[a] Clinical doses used in the selected clinical trials. Abbreviations: ER, endoplasmic reticulum; OS, oxidative stress; ROS, reactive oxygen species.

et al., 2012; Dehghan et al., 2013; Alluri et al., 2016), vascular processes (Kondoh et al., 2002; Kilic et al., 2004a; Hung et al., 2008), ameliorated the inflammatory response (Pei and Cheung, 2004; Lee et al., 2007) and reduced the degree of oxidative/nitrosative damage (Giusti et al., 1996a; Floreani et al., 1997; Sinha et al., 2001; Kondoh et al., 2002; Torii et al., 2004; Chen et al., 2006; Ozacmak et al., 2009; Yang et al., 2015). These beneficial effects were apparent following cerebral ischemia/reperfusion and were accompanied by an improvement of functional outcomes as well (Giusti et al., 1996b; Sinha et al., 2001; Lee et al., 2004; Kilic et al., 2008; Chen et al., 2009; Deykun et al., 2011).

Table 4 indicates that melatonin treatment in newborn animal stroke models was also very effective. Perinatal brain injury is associated mainly with inflammation, hypoxia-ischemia (HI) and formation of free radicals. Several studies indicate the efficacy of this neurohormone in attenuating cell death and brain injury thereby improving neuromorphophysiology (Welin et al., 2007; Carloni et al., 2008; Alonso-Alconada et al., 2012; Robertson et al., 2013). It was usually assumed that the antioxidant profile of melatonin was responsible of this protective effect against brain injury since there was a reduction in oxidative damage (Tutunculer et al., 2005; Signorini et al., 2009; Balduini et al., 2012). Neonatal HI encephalopathy affects the maturation of the auditory pathway; melatonin preserves functional integrity of the auditory pathway by reducing ROS damage (Revuelta et al., 2016). The neuroprotective effect of melatonin, furthermore, involves the attenuation of endoplasmic reticulum (ER) stress after neonatal HI (Carloni et al., 2014). The inflammatory response is also ameliorated after melatonin administration in HI rat models (Welin et al., 2007; Villapol et al., 2011; Balduini et al., 2012).

In the associated clinical trials, outcomes are not as positive after melatonin administration as in preclinical studies. As shown in Table 4, in newborn perinatal asphyxia animal models, even though the studies were RCTs, melatonin showed a good protective profile; in the animal models the outcomes where much more effective. This apparent discrepancy may be due to a low dosage of melatonin used in human newborns. Additionally, it should be noted that, chronologically, the development of normal sleep rhythm coincides with circadian variations in melatonin levels from the third to sixth month of life (Arendt, 2006). In humans, after birth, the first circadian rhythm of pineal melatonin synthesis and secretion occurs between the sixth and eighth week of life (Seron-Ferre et al., 2001). Obviously, a number of molecular processes remain to be explored relative to melatonin's efficacy as a stroke treatment.

When we extrapolated effective animal doses to humans, the results ranged from 25 to 100 mg, while the administered dose in the newborns was 10 mg. In the animal models, equivalent doses calculated ranged from 5- to 15-fold greater than the administered in RCTs. Human equivalent doses calculated for adults were also significantly greater than the administered in the RCTs. To better understand, we summarized and compared in Table 5 the melatonin outcomes reported in the 6 RCTs (see Table 1) and in the animal model studies (reported in Tables 3 and 4).

4. Discussion

This is the first systematic review that provides a comprehensive analysis of the evidence regarding the effectiveness of melatonin in stroke patients. We found six RCTs which met the criterion and which evaluate the therapeutic melatonin effects in stroke patients. Furthermore, we developed a comparative extrapolation of the doses used in RCTs to consider whether these correlate to the doses that would likely be effective in human patients.

To date, only six RCTs studied melatonin as a therapeutic agent in stroke or asphyxiated patients (Fulia et al., 2001; Aly et al., 2015; Dianatkhah et al., 2017; Ahmad et al., 2018; Grima et al., 2018; Zhao et al., 2018). Among them, three involved in newborns (Fulia et al.,

Table 5
Common melatonin treatment outcomes reported in the 6 RCTs and in the animal model studies.

Outcomes	Human	Animal
Oxidative stress regulation	(Fulia et al., 2001) (Aly et al., 2015) (Zhao et al., 2018)	(Chen et al., 2006) (Yang et al., 2015) (Giusti et al., 1996a, Giusti et al., 1996b, Uz et al., 1996, Floreani et al., 1997) (Ozacmak et al., 2009) (Sinha et al., 2001) (Tutunculer et al., 2005) (Balduini et al., 2012) (Revuelta et al., 2016) (Signorini et al., 2009)
Inflammation regulation	(Zhao et al., 2018)	(Pei and Cheung, 2004) (Lee et al., 2007) (Paredes et al., 2015) (Balduini et al., 2012) (Villapol et al., 2011) (Welin et al., 2007)
Survival rate improvement	Dianatkhah et al., 2017) (Ahmad et al., 2018)	(Kilic et al., 2008) (Giusti et al., 1996a, Giusti et al., 1996b, Uz et al., 1996, Floreani et al., 1997)
Neurodevelopmental outcomes improvement	(Aly et al., 2015)	(Kilic et al., 2008) (Lee et al., 2004) (Giusti et al., 1996a, Giusti et al., 1996b, Uz et al., 1996, Floreani et al., 1997) (Deykun et al., 2011) (Sinha et al., 2001) (Carloni et al., 2008)

2001; Aly et al., 2015; Ahmad et al., 2018) and three used adults (Dianatkhah et al., 2017; Grima et al., 2018; Zhao et al., 2018). The involved 278 stroke/hypoxic patients, from which 113 where adults and 145 newborns. These studies showed that melatonin treatment compared with placebo or non-treated patients (*i*) reduced oxidation and inflammation processes after stroke or asphyxia, (*ii*) improved survival rate in newborns and intubated stroke patients, (*iii*) regulated sleep and (*iv*) improved neurodevelopmental outcomes in asphyxiated newborns. After melatonin treatment in adults, there were no benefits reported regarding life quality. Such information would have been of great importance, given the dire consequences of stroke. Nevertheless, in one of the newborn studies, favorable neurodevelopmental outcomes were observed after treatment; these outcomes were evaluated at six months of age (Aly et al., 2015). Interestingly, no serious adverse effects were reported in any of these studies as consequence of melatonin treatment. Relative to information on the melatonin safety in literature, no melatonin safety conclusions can be drawn from the results on the RCTs (Seabra et al., 2000; Andersen et al., 2016; Foley and Steel, 2019).

There are some limitations to this review. These limitations included the small number of RCTs, uncertainty regarding blinding of participants and personnel, and a small number of patients. Additionally, the heterogeneity of measured outcomes limited general conclusions and made impossible direct comparisons or meta-analyses about the efficacy of melatonin in stroke.

As described in this systematic review, there are numerous reports in the scientific literature that document melatonin as an effective molecule in different *in vitro* and *in vivo* stroke models. The mechanisms by which melatonin exerts these protective effects are widely described in the literature; but, translational data for clinical studies are lacking. While this review reveals a lack of clinical studies the results that were reported were promising in the few RCTs carried out to date. No clinical trials of melatonin pretreatment have been reported, while in animals, highly protective results have been obtained when melatonin was used as a preventive therapy for ischemic brain injury (Pei and Cheung, 2004; Liu and Cheung, 2013; Li et al., 2014; Tang et al., 2014).

The pleiotropy of melatonin as a neuromodulator of inflammatory response, its ability to counteract free radical-mediated injury, regulate antioxidant activity and suppress excitotoxicity has been well-established (Manchester et al., 2015; Tan and Reiter, 2019). Considering the observations regarding tissue damage reduction, increased cell proliferation, and neurogenesis promotion, integrity and permeability of BBB maintenance, as well as its capacity of electrophysiological recovery improvement either alone or in combination with other therapeutic approaches, makes melatonin a suitable molecule, but unfortunately, not economically profitable option in stroke treatment. The small number of clinical trials with melatonin is likely due to its non-patentable nature (it is a natural product). Melatonin is inexpensive with a limited commercial margin. So, it has not attracted the interest of the pharmaceutical industry.

5. Conclusions

We found only six articles that include a RCT study of melatonin in stroke or asphyxiated patients; all of these provided evidence that melatonin treatment is a safe therapy with positive outcomes. Nevertheless, there is not sufficient available evidence to conclude that the clinical use of melatonin in these patients may be effective. Clearly, administered doses in subsequent RCTs should be reconsidered, inasmuch as the extrapolation of animal effective doses to humans as shown herein suggest the human doses used are likely far too low to significantly influence stroke outcomes in RCTs.

Financial support

This work was supported by UCJC (JEMELAR); and Fondo de Investigaciones Sanitarias (FIS)(ISCIII/FEDER) (Programa Miguel Servet CP14/00008; PI16/00735).

Declaration of Competing Interest

The authors declare no conflict of interest.

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