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TRANSCRANIAL PHOTOBIOMODULATION HELMET FOR MOTOR SIGNS OF PARKINSON'S DISEASE

EXECUTIVE SUMMARY

Transcranial photobiomodulation therapy (tPBMT) helmet refers to the delivery of laser photons using red (620–700 nm) and/or near-infrared (780–1270 nm) wavelengths of light through the scalp and skull to reach the underlying brain tissue leading to increase neuronal mitochondrial energy production (ATP synthesis), improve brain blood flow, reduce of brain β-amyloid load and deposition, attenuate dendrite and neuronal loss, and reduce inflammatory and oxidative neuronal injury. There was very limited evidence retrieved on transcranial photobiomodulation therapy helmet. It was claimed to have good safety profile, and improves all five subscore UPDRS-MDS-III (modified) results among responders. However, as being compared to sham, the only significantly improved score is the facial subscore in the intervention group. Larger clinical trials and cost-effectiveness study are needed to evaluate its efficacy before being used in Malaysian health facilities.

Keywords: neurodegenerative disease, low-level laser therapy, medical device

INTRODUCTION

Parkinson's disease (PD) is a progressive neurological disease, which is the second most common neurodegenerative disorder after Alzheimer's disease and the fastest growing neurodegenerative disease, due to an ageing population, a longer duration of the disease and possibly the increase in environmental contributors such as xenotoxins and environmental pollutants.[1]

Global estimates in 2019 showed over 8.5 million individuals with PD. Current estimates suggest that, in 2019, PD resulted in 5.8 million disability adjusted life years (DALYs), an increase of 81% since 2000, and caused 329 000 deaths, an increase of over 100% since

2000.[2] The largest number of PD patients was seen in the groups aged more than 65 years, and the percentage rapidly increased in the population aged more than 80 years.[3] Though the disease is more common in older people (affecting about 1% of people over the age of 60), but younger individuals can also be affected. It is slightly more common in men than women.[3]

It is a degenerative disease of the nervous system, affecting primarily the brain, but also other structures such as the peripheral autonomic nervous system.[4] The common motor problems of PD are rest tremor (although this is not present in all patients), bradykinesia and muscle rigidity. The diagnosis of PD is based on the presence of these motor problems. The bradykinesia of PD is often described by patients as a "weakness" of a hand or leg, but strength testing reveals no abnormalities. Imbalance (postural instability) with falls occurs only in the later stages of the disease. Most patients with early-stage PD experience motor symptoms on only one side of the body. However, it soon spreads to the other side but typically remains asymmetric throughout the disease course.[4]

THE TECHNOLOGY

Photobiomodulation therapy (PBMT), also known as low-level laser therapy (LLLT)[5] is a rapidly growing approach to the healing, stimulation, protection, and regeneration of many human organs and tissue types.[6] PBMT started in the 1960s as LLLT for wound healing, but since the introduction of light-emitting diodes (LEDs) has dramatically increased the number of applications and reports of positive results. Photobiomodulation therapy generally uses red (620–700 nm) and/or near-infrared (780–1270 nm) wavelengths of light at an intensity that causes no tissue heating, and its activity is based on well-established biological and cellular mechanisms.[6] Light-emitting diodes (LEDs) are light sources based on the semiconductor and have showed efficacy in different clinical conditions, mainly in the pain relief and reduction of inflammatory processes. LEDs produces important biological activities, such as synthesis of ATP, reduction of oedema and migration of inflammatory cells, decreased production of cytokines and inflammatory mediators. Several theories report that lasers are superior to LEDs because they generate coherent light and penetrate deeper than LEDs. The red light is able to penetrate enough to achieve 2–3 mm below the skin layers. Several studies have shown that LEDs and lasers with similar parameters produce equivalent effects. Studies have demonstrated the analgesic and anti-inflammatory effect of red LED in different pathological conditions, such as: treatment of burn wound, knee osteoarthritis, Achilles tendinopathy, hip arthroplasty, oral mucositis, hemicontusion spinal cord injury and pain after surgery.[7]

Transcranial photobiomodulation therapy (tPBMT) refers to the delivery of laser photons through the scalp and skull to reach the underlying brain tissue. Multiple molecular mechanisms of action for tPBMT include increased neuronal mitochondrial energy production (ATP synthesis), improved brain blood flow, reduction of brain β-amyloid load and deposition, attenuation of dendrite and neuronal loss, and reduced inflammatory and oxidative neuronal injury.[8] It was discovered some time ago that the principal chromophores (light-absorbing molecules) are located within the mitochondria. Cytochromes are involved in several units of the respiratory chain (including cytochrome c oxidase), and they can absorb red/near-infrared light thus increasing electron transport and the mitochondrial membrane potential to increase adenosine 5'-triphosphate production. The raised mitochondrial membrane potential leads to a brief burst of reactive oxygen species in normal cells, but in dysfunctional mitochondria, the normalisation of the mitochondrial membrane potential reduces the generation of reactive oxygen species and mitigates oxidative stress. There are also increases in nitric oxide and intracellular calcium, along with the activation of numerous transcription factors.[6]

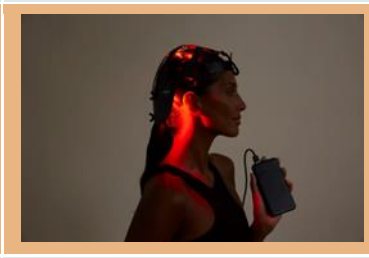
The use of tPBM has been explored in translational models of neurodegenerative and neurological diseases such as Alzheimer's disease, traumatic brain injury, stroke, and anxiety/depression.[9] Malaysian Health Technology Assessment Section (MaHTAS) had assessed one of photobiomodulation therapy which is indicated for Alzheimer's disease, called GammaSense.[10]

However, there is still a divergence of results because the lack of guidelines and protocols on red LED or Laser dosage, duration and frequency for specific disorders.[7]

PBM devices used as adjunctive devices for the temporary relief of pain have been cleared for marketing by FDA through the Premarket Notification/510(k) process.[11] Transcranial PBMt for Parkinson Disease has yet to be approved by USFDA. There are various commercialised transcranial photobiomodulation therapy helmet in the market for various indications such as Alzheimer's disease, as shown in Table 1.[12-15]

Table 1 Examples of commercialised transcranial photobiomodulation therapy helmet

Commercialised Transcranial PBMt	Indication	Light wavelength	Image

Suyzeko's Photobiomodulation Therapy Helmet Services	traumatic events (stroke, traumatic brain injury, and global ischemia), degenerative diseases (dementia, Alzheimer's and Parkinson's), and psychiatric disorders (depression, anxiety, post traumatic stress disorder).	810nm infrared light NIR LED	
SYMBYX Neuro	Motor symptoms of Parkingson Disease	20 Red light LEDs of 635nm, 20 Infra-red light LEDs of 810nm	
Neuradiant 1070	Cognitive function (no diagnosis specified on official website)	1070nm wavelength LED	
Domer Laser Therapy Helmet	Dementia, Parkinson's, Alzheimer's Disease	810nm Infrared Red Light	

SYMBYX Neuro helmet, purposely designed for treating symptoms of PD consists of 40 diodes that delivered 12 min of red light (20 × 635 nm LEDs) followed by 12 min of infrared light (20 × 810 nm LEDs). A total of 37.44 and 19.44 joules were delivered from each of 20 diodes, providing a total of 1137 joules administered each session.[9]

PATIENT GROUP AND INDICATION

Transcranial photobiomodulation therapy helmet for improvement of motor signs of Parkinson's disease.

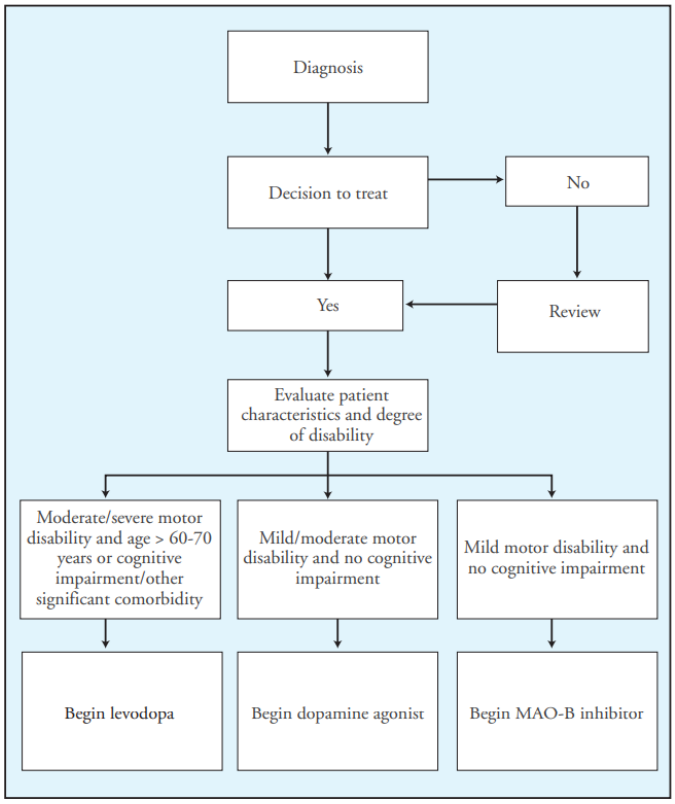
CURRENT PRACTICE

There is no test (during life) currently that can definitely identify PD. The diagnosis of PD is based on the history and a careful neurologic examination. There is currently no cure (or prevention) for PD, and the disease worsens gradually over years. Nevertheless, motor symptoms can often be well controlled with treatment, especially in the earlier stages of the disease. At present, these treatments are mainly based on restoring dopaminergic stimulation in the brain.[4]

Pharmacological option is initiated based on patient characteristics and degree of disability, as shown in Figure 1.[4] The medications currently used to treat PD provide symptomatic benefit, which means reducing PD symptoms such as tremor, bradykinesia and rigidity.[4] The options are:

1. Levodopa (L-dopa)
2. Dopamine agonists.
    a. Ergot dopamine agonists (e.g: Bromocriptine)
    b. Non-ergot dopamine agonists (e.g: Piribedil, Ropinirole, Rotigotine, Pramipexole)
3. MAO-B Inhibitor (e.g: Selegiline, Rasagiline)
4. Anticholinergic agents (e.g: Trihexyphenidyl or Benzhexol, Orphenadrine)

Figure 1 shows decision pathway for the initiation of medication treatment for PD[4]



*MAO-B: type-B monoamine oxidase

Non-pharmacologic management include physiotherapy (stretching and strengthening exercises, gait and balance training including use of cueing techniques, etc.), occupational therapy (rehabilitation techniques that help maximise functional capacity through lifestyle adaptations and possible use of assistive devices; this may include assessment of safety in the home environment, e.g., installation of grab rails, shower seats, etc.), speech therapy (rehabilitation techniques to strengthen speech for improved communication, and to improve efficiency of swallowing which may reduce the risk of aspiration), and advice from a dietitian (unintended weight loss is a common feature of PD).[4]

EFFICACY AND SAFETY

Systematic search was conducted from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines [Google Scholar and US Food and Drug Administration (US FDA)] on Transcranial Photobiomodulation Helmet in Parkinson's Disease.

There was **two** published scientific evidence on effectiveness of Transcranial Photobiomodulation Helmet in Parkinson's Disease.

Efficacy

A triple-blinded, randomised placebo-controlled trial, recruited 40 idiopathic PD patients with Modified Hoehn and Yahr Stage I–III, aged 59–85 years who was on stable anti-PD medications. The participants received either active tPBM (635 nm plus 810 nm LEDs) or sham tPBM for 24 min per day (56.88J) for six days per week for duration of 12 weeks. The primary outcome measures were treatment safety and a 37-item subscore MDS-UPDRS-III (motor domain) assessed at baseline and 12 weeks. The trial was conducted remotely due to COVID-19 pandemic. Participants received their tPBM device (active or sham) by mail and were instructed on how to apply the treatment via internet-based video conferences to ensure correct device fitment and operation. The MDS-UPDRS-III was collected and documented using a visual assessment obtained via Zoom video link. Each participant had a 'carer' that was able to manipulate the camera to ensure that the assessor had an optimal view. Each participant was re-assessed by the same assessor.[16]

The result as shown in Figure 3 indicated that total MDS-UPDRS-III scores improved significantly in both the treatment group (p = 0.011) and the sham group (p = 0.010) with a mean improvement of 23% and 24% above the baseline score in the treatment and sham groups, respectively. The facial sub-score was significantly improved in the treatment group (p = 0.008) but not the sham group (p = 0.076), while the gait sub-score was significantly improved in the sham group (p = 0.046) but not the treatment group (p = 0.102). Both groups showed statistically significant improvement in the lower-limb sub-score (treatment p = 0.017; sham p = 0.007).[16]

Figure 2 UPDRS-MDS-III (modified) results of all participants[16]

	Group	Baseline Mean (SD)	12-Week Mean (SD)	Mean Difference	Paired *t*-Test		
					Mean % Improvement	T Score	*p* Value
UPDRS scores for all participants (df: active = 19; sham = 17)							
Total score	Active	21.35 (9.43)	16.45 (9.48)	−4.90 (7.67)	23%	2.84	0.010 *
	Sham	26.00 (13.81)	20.47 (12.83)	−5.52 (7.93)	21%	2.85	0.011 *
Facial	Active	2.26 (1.44)	1.73 (1.66)	−0.53 (0.77)	23%	2.92	0.008 *
	Sham	2.24 (1.44)	1.88 (1.49)	−0.36 (0.93)	16%	1.56	0.138
Upper limb	Active	6.63 (3.53)	4.84 (3.82)	−1.79 (3.88)	27%	1.84	0.060
	Sham	7.24 (4.68)	6.59 (4.87)	−0.64 (3.37)	9%	0.79	0.440
Lower limb	Active	4.26 (2.51)	2.47 (2.38)	−2.26 (2.62)	53%	2.61	0.017 *
	Sham	6.24 (3.68)	3.88 (2.29)	−2.36 (3.16)	38%	3.04	0.007 *
Gait	Active	3.37 (1.54)	2.79 (1.87)	−0.58 (1.46)	17%	1.87	0.102
	Sham	5.00 (2.80)	3.65 (2.85)	−1.35 (2.57)	27%	2.16	0.046 *
Tremor	Active	4.84 (3.48)	4.11 (2.96)	−0.74 (2.58)	15%	0.51	0.229
	Sham	5.29 (5.59)	4.47 (4.45)	−0.82 (3.6)	16%	0.93	0.361

Source: McGee C, Liebert A, Bicknell B, et al. A Randomized Placebo-Controlled Study of a Transcranial Photobiomodulation Helmet in Parkinson's Disease: Post-Hoc Analysis of Motor Outcomes. J Clin Med. 2023;12(8).

Figure 3 UPDRS-MDS-III (modified) results of responders.[16]

UPDRS scores for responders (df: active = 13; sham = 9)							
Total score	Active	22.86 (10.39)	14.57 (8.87)	−8.29 (5.17)	36%	6.00	<0.001 *
	Sham	29.80 10.39)	18.80 (14.31)	−11.00 (2.98)	37%	11.67	<0.001 *
Facial	Active	2.07 (1.38)	1.50 (1.51)	−0.57 (0.76)	28%	2.83	0.014 *
	Sham	2.10 (1.52)	1.50 (1.43)	−0.60 (0.97)	29%	1.97	0.081
Upper Limb	Active	7.07 (3.73)	4.29 (3.58)	−2.79 (3.89)	40%	2.68	0.019 *
	Sham	8.30 (5.31)	6.30 (5.25)	−2.00 (2.91)	24%	2.18	0.058
Lower Limb	Active	4.29 (2.73)	1.79 (2.12)	−2.50 (2.41)	58%	3.88	0.002 *
	Sham	7.60 (3.57)	3.70 (2.41)	−3.90 (2.57)	51%	4.82	0.001 *
Gait	Active	3.57 (1.40)	2.57 (1.79)	−1.00 (1.24)	28%	3.01	0.010 *
	Sham	5.60 (2.99)	3.60 (2.91	−2.00 (2.98)	36%	2.12	0.063
Tremor	Active	5.86 (3.39)	4.43 (3.03)	−1.43 (2.34)	24%	2.28	0.040 *
	Sham	6.20 (6.51)	3.70 (4.53)	−2.50 (3.63)	40%	2.18	0.057

Figure 4 shows all five clinically relevant sub-scores significantly improved in the treatment group, with improvements of between 24% and 58%. (Source: McGee C, Liebert A, Bicknell B, et al. A Randomized Placebo-Controlled Study of a Transcranial Photobiomodulation Helmet in Parkinson's Disease: Post-Hoc Analysis of Motor Outcomes. J Clin Med. 2023;12(8).)

Societal/ethical

There was no retrievable evidence on societal or ethical issue on Transcranial Photobiomodulation Helmet in Parkinson’s Disease.

Safety

According to previous trial mentioned, the safety of tPBM was established over the 12 weeks of the study, with no SAEs attributable to the treatment. The treatment was well tolerated, and compliance was excellent, with no withdrawals from the treatment group and three from the sham group.

Another published study is a double-blinded, randomised, sham-controlled feasibility trial involving patients aged 59–85 years with idiopathic PD and were treated with a tPBM helmet for 12 weeks (72 treatments with either active or sham therapy; stage 1). Treatment was delivered in the participants' homes, monitored by internet video conferencing (Zoom). Stage 1 was followed by 12 weeks of no treatment for those on active therapy (active-to-no-treatment group), and 12 weeks of active treatment for those on sham (sham-to-active

group), for participants who chose to continue (stage 2). The active helmet device delivered red and infrared light to the head for 24 min, 6 days per week. The primary endpoints were safety and motor signs, as assessed by a modified Movement Disorders Society revision of the Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III). The number of participants who chose not to continue produced a disparity between the numbers in each group during stage 2 (20 vs 12). Treatment was well tolerated and feasible to deliver. Of the nine suspected adverse events that were identified, two minor reactions may have been attributable to the device in the sham-to-active group during the active treatment weeks of the trial. One participant experienced temporary leg weakness. A second participant reported decreased fine motor function in the right hand. Both participants continued the trial.[9]

ESTIMATED COST

The price of already commercialised transcranial photobiomodulation therapy helmet ranges from RM5000 to RM17273 for various indications. The wavelength used in each technology are also differs.[13-15] There was no cost-effectiveness study or cost analysis study retrieved on transcranial photobiomodulation therapy helmet.

POTENTIAL IMPACT

In conclusion, there was very limited evidence retrieved on transcranial photobiomodulation therapy helmet. It was claimed to have good safety profile, and improves all five subscore UPDRS-MDS-III (modified) results among responders. However, as being compared to sham, the only significantly improved score is the facial subscore in the intervention group. Larger clinical trials and cost-effectiveness study are needed to evaluate its efficacy before being used in Malaysian health facilities.

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