

Impact of yoga based lifestyle intervention on psychological stress and quality of life in the parents of children with retinoblastoma

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KEY WORDS

Childhood cancer
Depression
Quality of Life
Retinoblastoma
Yoga based lifestyle intervention

ABSTRACT

Background: Childhood cancers are associated with a psychological burden to the parents and hence, decline their mental and physical health and overall quality of life.

Purpose: The purpose of the present study is to investigate the impact of 12-weeks yoga based lifestyle intervention on psychological stress and quality of life in the parents of children affected with retinoblastoma.

Method: Single arm prospective clinical trial conducted from October 2015 to October 2017 at the Laboratory for Molecular Reproduction and Genetics, Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India. A pre-tested 12-weeks yoga based lifestyle intervention included asanas (physical postures), pranayama (breathing exercises), dhyana (meditation), relaxation techniques, lectures and films on yoga, interactive sessions and individualized advice was administered to the participants.

Results: 12-weeks of yoga based lifestyle intervention programme leads to a significant improvement in psychological stress and overall quality of life in the parents of retinoblastoma patients. There was a significant improvement in all the domains (physical health, psychological health, social relationships, and environment) of WHOQOL-BREF from baseline (day 0) to 12-weeks of yoga based lifestyle intervention. Yoga based lifestyle intervention also led to a significant increase in the levels of brain derived neurotrophic factor, dehydroepiandrosterone sulphate, sirtuin 1 and decreased the cortisol and IL-6 levels.

Conclusion: Yoga based lifestyle intervention reduced the severity of psychological stress and resulted in improvement in overall quality of life and upregulation in levels of systemic biomarkers of neuroplasticity. YBLI may serve as a beneficial therapy and may also act as an effective medium for better stress management to develop better coping strategies in the parents of retinoblastoma patients.

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Introduction

Despite improvement in the available treatment options and increase in cure and survival rates, many forms of childhood cancers are still considered as chronic illnesses and if detected later, have a poor prognosis. Any form of childhood cancer, the second most leading cause of death among children below 5 years of age is associated with psychosocial, psychosomatic, emotional and physical stress for the family caregivers, especially for the parents [1, 2]. Numerous studies have also reported that family caregivers of cancer patients quite often experience elevated levels of symptoms of depression, anxiety, social isolation, sleep disturbances, fear and hopelessness [3]. Henceforth, the family caregivers experience a substantial extent of distress in their efforts to provide care for the cancer patient [4]. This distress is associated with a decline in the capacity to do daily activities as well as in the quality-of-life (QOL) in the parents of children who had suffered or are suffering from any form of cancer. The World Health Organization (WHO) has defined "QOL" as the perception of the person re-

garding life in the context of cultural and environmental systems and in relation to one's objectives, beliefs and expectations. It reflects the biological modifications and the impact of interventions at a personal level [5]. The psychosomatic stress in the parents of the children with cancer affect their family functioning, well-being of the healthy sibling, their work as well as social life [6]. The persistent depressive symptoms in the parents of children with cancer are also an indication of increased biological susceptibility of these post-traumatic stress symptoms in the child with cancer [7]. The severity of stress symptoms in the parents are variable and depend upon the severity of the cancer in the child. These symptoms are found to be variable during the course of disclosure of cancer diagnosis in the children, initial course of treatment, follow-up and side effects associated with the cancer treatment (chemotherapy, radiation therapy, etc.), post-treatment and recurrence [8].

Retinoblastoma is an aggressive cancer of the primitive retina and comprises 4% of all the childhood malignancies [9]. The incidence of retinoblastoma is 1 case in every

15,000–20,000 live births translating to nearly 9,000 newly reported cases every year worldwide [10, 11]. In India, the incidence of retinoblastoma has drastically increased over the past two decades leading to 1800 newly diagnosed cases every year which is mainly attributed to increased awareness of the disease among the parents, improvement in the healthcare system in India over the past decade and better prognosis due to improvement in diagnostic measures [12]. Nonetheless, despite high cure rates, advancements in therapeutics and supportive care, initial diagnosis of retinoblastoma brings psychosocial burden and stress to the parents. In addition to this, enucleation is considered as a cosmetic infirmity to the child which is treated as a deterrent to the marriage prospect [13]. Willard *et al.* assessed the association between parenting stress in the caregivers of retinoblastoma patients and child outcomes. They have found that baseline parenting stress contribute to changes in the child's functioning over time [14]. All these above-mentioned factors are associated with a decline in the QOL of the family caregivers (parents) and are further associated with parent's enhanced risk to the psychiatric ailments due to on-going stress in relation to their child's illness [15].

Mind-body interventions such as yoga based lifestyle intervention (YBLI) is recognised as an adjunct to modern medicine and have been profoundly used to treat many medical conditions including stress and lifestyle related disorders, chronic inflammatory disorders and metabolic syndromes [16]. YBLI improves cellular health and mind-body communications which optimizes brain health by improving neurotransmitter homeostasis, circadian rhythm, neuroplasticity, and neural networks. These biological processes increases stress resilience, improves overall health and QOL [17]. Recently published studies have described the positive impact of short-term (12-weeks) practice of YBLI on neural cognition and neural plasticity and decline in the depressive symptoms in the patients of major depressive disorder (MDD) [18–20]. YBLI also decreases oxidative stress, inflammation and various cellular stress markers and positively impact germ cell integrity and normalize sperm transcripts levels which may improve health trajectory of the next generation [21]. YBLI also improves sperm DNA integrity and reduces mutation load and may reduce *de novo* germ line and post-zygotic mutation burden. Thus, this may reduce genetic and epigenetic disease burden in the offspring [22, 23].

Interventions that leads to long-term improvement in biomarkers of neuroplasticity such as brain derived neurotrophic factor (BDNF), dehydroepiandrosterone sulphate (DHEAS), sirtuin1, cortisol and Interleukin-6 (IL-6) are essential for healthy individuals as well as patients with neuropsychiatric ailments [20, 24, 25]. Very few studies in the literature have focussed on the psychological stress in the parents of children with retinoblastoma [14, 26–29]. In a developing country like India where the incidence of retinoblastoma is quite high (6–10% of all childhood cancers) as compared to developed nations (incidence being 2.5–4% of all childhood cancers) and advanced form of retinoblastoma contributes

to nearly 35–40% of all the cases, no studies have reported the psychosomatic illness in the parents' of retinoblastoma children in the Indian scenario [30]. Studies delineating the impact of YBLI (which is a definite warrant to expedite stress coping and overall health) on the improvement of cellular stress biomarkers as well as on the QOL in the parents of retinoblastoma patients are lacking in the literature. With this background in mind, the primary outcome of the present study was to evaluate the impact of YBLI on psychological stress in the parents of retinoblastoma patients using Beck depression inventory-II (BDI-II) Scale and assessment of QOL using World Health Organization QOL (WHOQOL-BREF). The secondary outcome of the study was to investigate the pre and post-YBLI levels of systemic biomarkers of neuroplasticity such as BDNF, DHEAS, sirtuin1, cortisol and IL-6.

Methods

Study design

The study was conducted between October 2015 and March 2017. This was a single arm prospective clinical trial to determine the pre and post impact of 12-weeks of YBLI in the parents of children affected with retinoblastoma. The study was initiated after approval from Institute's Ethics Committee (ESC/T-370/22-07-2015) and after obtaining registration of the clinical trial; Clinical Trial Registry of India (CTRI) REF/2014/09/007532. Signed informed consent was also obtained from all the participants.

Participants

The participants include parents of retinoblastoma patients (N = 86; 46 males and 40 females; age 31.38 ± 7.3 years) who wished to join the intervention and were recruited from the Ocular Oncology Service, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences (AIIMS), New Delhi (a tertiary research and referral centre with the highest referrals for retinoblastoma). The mean age of the retinoblastoma patients whose parents were enrolled for the present study was 3.8 ± 1.3 years.

The inclusion criteria for the participants were the following: a) a confirmed diagnosis of retinoblastoma in their child should have been made by the ophthalmologist at the time of starting the study b) the participants should have a good understanding of Hindi or English in order to answer the questions in the psychological screening questionnaire c) the participants shouldn't have any systemic illness and shouldn't have any history of psychiatric ailment d) the participants shouldn't have participated in any clinical trial/study 4 months prior enrolling them for the YBLI. The exclusion criteria included physically challenged individuals and those who were unable to perform the intervention exercises.

Yoga based lifestyle intervention

The parents of the retinoblastoma patients were enrolled in the study within 1 year of retinoblastoma diagnosis in the child.

Eligible subjects were enrolled in the study after screening and baseline characteristics were recorded. The participants underwent a 12-week pre-tested YBLI program comprising of theory and practice sessions. Details of activities of the YBLI program which were specially designed and standardized for the patients of MDD were taken from the study previously published from our laboratory [20]. We have followed the same protocol with slight modifications. The complete YBLI program is mentioned in table 1. YBLI consists of five sessions per week. For the first two weeks, the sessions were held at the Laboratory for Molecular Reproduction and Genetics, Department of Anatomy, AIIMS, New Delhi under the supervision of registered and qualified yoga instructor. For the remaining 10 weeks, the participants were instructed to do yoga at their homes. Regular monitoring of the home based YBLI was maintained through diary and telephonic contact.

Table 1: Details of activities of the Yoga based Lifestyle Intervention (YBLI) program.

1.	Session preparation instructions	2 min
2.	Prayer with OM chanting	10 min
3.	Loosening practices (warm up)	10 min
4.	Sun salutation	5 min
5.	Asanas (Postures)	
	Supine-Shawasana	2 min
	Uttanpadasana	2 min
	Pawanmuktasana	2 min
	Setubandhasana	2 min
	Prone-Makarasana	2 min
	Shalabhasana	2 min
	AdhomukhShvanasana	2 min
	Dhanurasana	2 min
	Sitting-Baddha Konasana	2 min
	Yog Mudrasana	2 min
	Pashchimottanasana	2 min
	Ushtrasana	2 min
	Standing-Tadasana	2 min
	Vrikshasana	2 min
	Ardhachakrasana	2 min
6.	Relaxation-Shavasana	7 min
7.	Pranayama (Breathing exercises)	
	Kapalbhati	35 min
	Bhastrika	
	Ujjayi	
	Nadishodhana	
	Bhramari	
8.	Recitation of OM	
9.	Dhyan (Meditation) with positive auto-suggestion	10 min
10.	Shanti Mantra	5 min
11.	Interactive session/Self-directed learning	20 min
	Total Duration:	134 min

Each session in YBLI comprises a set of asanas (physical postures), pranayama (breathing exercises), and dhyana (meditation) for approximately 90 minutes. This was followed by interactive sessions, lectures and films on yoga, discussion on principles of yoga and yogic techniques, stress management, individualized advice (only during the first two weeks of YMLI at Laboratory for Molecular Reproduction and Genetics, Department of Anatomy). The participants were also encouraged to accommodate these healthy lifestyle changes in their day to day life even after the completion of the study for the long term benefits of YBLI.

Outcome measures

Primary Outcomes

The primary outcome was pre-and-post assessment of psychological stress and QOL in the parents of retinoblastoma patients. The following two measures were used for this:

Beck depression inventory-II (BDI-II) scale: The severity of psychological stress was measured using BDI-II scale at baseline (day 0) and after 12 weeks of YBLI. BDI-II is one of the most widely used psychometric tests for measuring the severity of depression according to the diagnostic criteria listed in the Diagnostic and Statistical Manual for Mental Disorder-V (DSM-V) [31]. This original BDI instrument was developed in 1961 by Beck *et al.* [32]. BDI-II which was published in 1996 has a considerable revision of the original and revised BDI-IA scale. BDI-II consists of 21-item self-report multiple-choice inventory and takes ~10 minutes to complete. It is available in multiple languages, and monitors change over time. It differentiates the severity of depression based upon the following score ranges: minimal range = 0–13, mild depression = 14–19, moderate depression = 20–28, and severe depression = 29–63 [33, 34].

WHOQOL-BREF: WHOQOL-BREF questionnaire was administered at baseline (day 0) and after 12 weeks of YBLI. This questionnaire assesses the individual's perceptions in the context of their culture and value systems, and their personal goals, standards and concerns [35]. Translated and validated version of WHOQOL-BREF in Hindi was also made available. WHOQOL-BREF questionnaire comprises 26-items and produces scores in four broad domains related to QOL (D1: physical health; D2: psychological health; D3: social relationships; and D4: environmental). Physical health is having 7 items (D1), psychological health is with 6 items (D2) social relationships with 3 items (D3) and environmental health with 8 items (D4). Answers to all questions were rated on a 6-point Likert scale, yielding 4 scores relating to the 4 domains. According to the guidelines recommended by the WHO study group on WHOQOL-BREF, the score for each domain was transformed into a 0–100 score, in which a higher score denotes higher QOL (domain scores are scaled in a positive direction) [36]. In addition to these four domains, there are two global questions (Overall rating of QOL and Overall satisfaction with health) which are to be reported separately.

Secondary outcomes

The secondary outcome included pre-and-post evaluation of blood biomarkers of neuroplasticity which included: the cardinal biomarker of neuroplasticity i.e., BDNF and mind-body communicative biomarkers such as- DHEAS, sirtuin1, cortisol and IL-6. For the laboratory assessment of these biomarkers, fasting venous blood samples (5 mL) were collected at the start (day 0) and at the end of intervention (blood samples were withdrawn early in the morning prior to breakfast and participants were also encouraged not to get involved in any physical activity/exercise before acquisition of the blood samples in the morning). One part of the blood was allowed to clot, and the serum was separated within 30 minutes, and the other part was transferred to heparinized and EDTA vials and was centrifuged at 2000 *g* for 15 minutes at 4°C. Both serum and plasma were stored at -80°C until analysed. The blood biomarkers were estimated using commercially available enzyme-linked immunosorbent assay (ELISA) kits for estimating the levels of BDNF (Raybiotech, Inc), sirtuin 1 (Qayee Bio-Technology), DHEAS (Qayee Bio-Technology), cortisol (DRG Diagnostic, Germany), and IL-6 (Gen-Probe, Diaclone Diagnostic, France). Quality-control assays were taken for the biomarkers, and methods were validated.

Statistical analysis

Data were analysed using the GraphPad Prism (Version 8) software. Pre- to post-intervention changes were evaluated using paired *t*-tests for continuous variables, or Wilcoxon signed rank test for continuous variables without normal distribution. Odds ratio (OR) were calculated and reported within 95% confidence interval (CI) using a calculator for CIs of OR based upon the null hypothesis (<http://www.hutchon.net/ConfidORnulhypo.htm>). A *p*-value of <0.05 was considered as statistically significant.

Results

The mean age of the participants (parents of retinoblastoma patients) who participated in the study and underwent YBLI was 31.38 ± 7.3 years (46 males and 40 females). The mean BMI of the participants is 27.19 ± 4.6 kg/m². The flow diagram regarding participant's enrolment for YBLI is described in figure 1. The socio-demographic characteristics of the participants are summarized in table 2.

BDI-II scores were assessed in the participants (parents of retinoblastoma patients) at day 0 and after 12-weeks of YBLI. There was a significant decline in the BDI-II scores from baseline to 12-weeks of YBLI (*p*<0.0001) (figure 2).

WHOQOL-BREF questionnaire was also assessed in the participants at day 0 and after 12-weeks of YBLI. The participants showed significant improvement in the overall rating of QOL and overall satisfaction with health from baseline to 12-weeks of YBLI (*p*=0.0020 and *p*=0.0072 for overall rating of QOL and overall satisfaction with health respectively) (figure 3). There was also a significant improvement in all the four domains of WHOQOL-BREF from baseline to 12-weeks

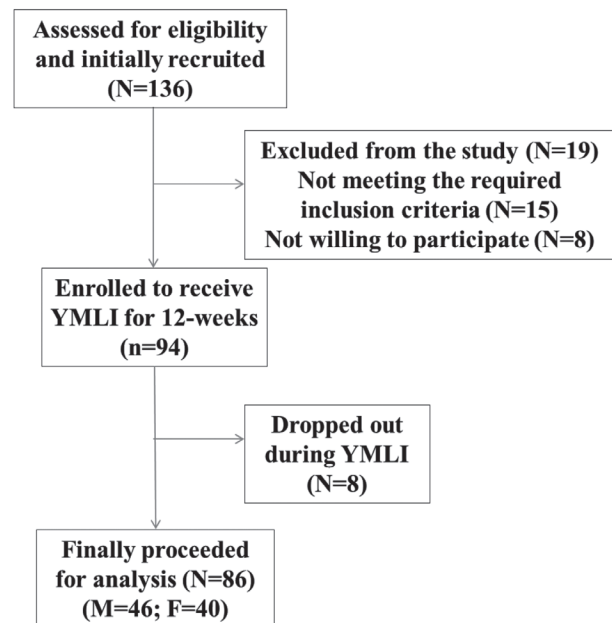


Fig. 1: Flow diagram of participant enrolment for YBLI. (M: Males; F: Females).

Table 2: Demographic characteristics of participants (parents of retinoblastoma patients).

Socio-demographic characteristics	Total participants (N = 86)
Age (years)	31.38 ± 7.3
BMI (kg/m ²)	27.19 ± 4.6
Education, n (%)	
Matric	39 (45.34)*
Intermediate	43 (50)
Graduate	3 (3.49)
Post-graduate and above	1 (1.16)
Religion, n (%)	
Hindu	59 (68.60)
Muslim	22 (25.58)
Sikh	01 (1.16)
Christian	04 (4.65)
Others	0
Habitat, n (%)	
Rural	22 (25.58)
Urban	64 (74.41)
Employment status, n (%)	
Employed	48 (55.81)
Unemployed	38 (44.18)
Income group, n (%)	
Upper class	02 (2.32)
Upper middle class	04 (4.65)
Lower middle class	12 (13.95)
Lower class	68 (79.06)
Lifestyle habits	
Smoker, n (%)	
Ever smoker	01 (1.16)
Former smoker	01 (1.16)
Current smoker	02 (2.32)
None	82 (95.34)

Socio-demographic characteristics	Total participants (N = 86)
Drinker, n (%)	
Ever drinker	01 (1.16)
Former drinker	02 (2.32)
Current drinker	18 (20.93)
None	65 (75.58)
Self-rated health, n (%)	
Excellent	0
Good	0
Fair	38 (44.18)
Poor	48 (55.81)

BDI-II scores pre and post YBLI

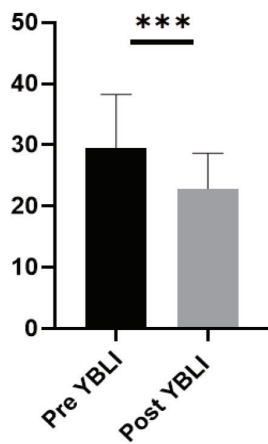


Fig. 2: Pre and post comparison of BDI-II scores in the participants (parents of retinoblastoma patients).

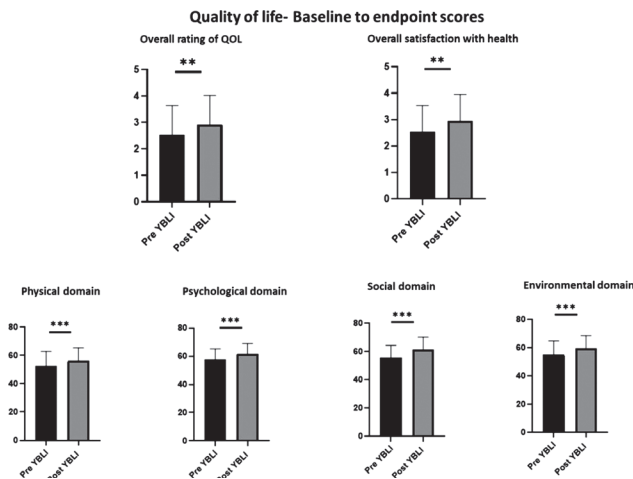


Fig. 3: Baseline to endpoint measures of quality of life scores in WHO-QOL-BREF scale. (***) $P < 0.001$.

of YBLI. This shift in WHOQOL-BREF questionnaire scores from baseline to 12-weeks was found to be statistically significant for all the domains (D1: $p < 0.0001$; D2: $p < 0.0001$; D3: $p < 0.0001$; and D4: $p < 0.0001$) (figure 3).

The trend in the levels of blood biomarkers of neuroplasticity pre-and-post YBLI were as follows. There was a significant increase in BDNF (ng/mL) levels ($p < 0.0001$) (cardinal biomarker of neuroplasticity) at the end of the intervention (12-weeks) versus baseline (day 0). Regarding the mind-body communicative biomarkers, DHEAS and sirtuin 1 were found to be significantly increased ($p < 0.001$ and $p < 0.0001$ for DHEAS and sirtuin 1 respectively) following the intervention. Cortisol and IL-6 were found to be significantly declined ($p < 0.0001$ and $p = 0.004$ for cortisol and IL-6 respectively) at the end of the intervention (12-weeks) versus baseline (day 0) (table 3).

Discussion

Family caregivers of cancer patients are highly susceptible to psychological stress and hence showed deterioration in overall QOL in their attempt to provide caregiving for the cancer patients [4]. QOL is a quantitative as well as qualitative measurement that can identify groups with physical or mental health problems and provide a guide to intervention and follow-up evaluation. Two lakh new diagnosed cases of childhood cancers were annually reported worldwide of which more than 80% belong to the low to middle income countries [37]. Despite advancements in therapeutics and development of multi modal therapies for cancer treatment, childhood cancer is the second most common cause of death among children and hence, considered a major burden to the health-care system.

Initial diagnosis of cancer in the child brings distress and psychological stress symptoms in the family caregivers (parents) as they have to cope up with a wide array of physical, social, emotional and financial burden in course of the treatment and disease progression in the child [38]. Growing body of evidences have reported that initial stress symptoms (anxiety, depression and posttraumatic stress symptoms) that have been reported in the parents of childhood cancers may decline during the treatment administration to their child [39, 40]. The parental distress is associated with a decline in overall QOL (reduced mental as well as physical health) and thus, further decline the caregiving to the child suffering from cancer [41]. The parental distress is also determined by the type of cancer in the child, administered therapy, time to cure and cancer remission. The psychological stress symptoms in the parents also aggravate due to decline in their social life/social responsibilities, decline in their job performance and economic issues faced by them due to adherence to a complicated treatment regimen during their child's treatment. There are plethora of studies conducted which suggested psychological stress and increased risk of neuropsychiatric ailments in the parents of children affected with cancer when compared to the parents of healthy children. Thus, cancer in the child affects the whole family functioning and parents may be considered as "hidden patients" [42]. A meta-analysis was conducted by Pai et al. on 29 previously published studies examining psychological

Table 3: Pre-and Post YBLI comparison of blood biomarkers of neuroplasticity.

Biomarkers for neuronal plasticity	Baseline (Day 0)		Post-yoga (12-week)		Change from baseline to 12-week Mean [95% CI]		p-value within group
	Mean	SE	Mean	SE	Mean	CI	
BDNF (ng/ml)	13.08	.795	20.35	1.278	-7.27	-9.49, -5.89	<0.0001
Cortisol (ng/ml)	409.95	5.074	276.23	32.63	133.72	68.10, 199.34	<0.0001
IL-6 (pg/ml)	3.87	.097	2.69	.195	1.18	0.43, 2.76	0.005
Sirtuin 1 (ng/ml)	32.01	.53	39.22	1.190	-7.203	-9.36, -5.03	<0.0001
DHEAS (ng/ml)	67.66	.35	79.47	1.267	10.57	5.97, 16.74	<0.001

distress and marital and family functioning among parents of children with cancer. The authors concluded that paediatric cancer impacts parent's perceptions of self and family functioning, especially within the 1st year following diagnosis and mothers of children affected with cancer experience greater distress and higher family conflicts when compared to the mothers of healthy children [15]. The mode of action of yoga is mediated through improving the cardiac vagal tone, activation of parasympathetic system and via reducing the activation of hypothalamo-pituitary-adrenal (HPA) axis which is hyper-activated during perceived stress. This in turn leads to immune system modulation and homeostasis, improvement in overall metabolic and psychological profiles and thereby, reduces the perception of stress [16, 43].

The present study assessed the impact of 12-weeks YBLI on the QOL in the parents of children who have been recently diagnosed with retinoblastoma. The results showed significant improvement in the overall rating of QOL and overall perception of health at the end of the intervention verses baseline (day 0) in these participants. A significant improvement has been noted in all the domains (physical, psychological, social, and environmental) of WHOQOL-BREF. The improvement in QOL was also found to be collateral with the improvement in the biomarkers of neuronal plasticity. A growing body of recent evidences showed that mindfulness-based psychosocial interventions such as YBLI have an important role in reducing the symptoms of psychiatric disorders and have shown most promising evidence in depressive disorders as it improve neuroplasticity and reduces markers of psychological and oxidative stress. YBLI have proven itself as an important adjunct to modern medicinal practices and serve as an adjunctive treatment regimen for a number of psychiatric conditions [44]. It is especially useful in psychological stress as it increases concentration, calmness, attention, awareness, and alleviates mood [45]. It increases brain alpha and theta waves [46].

In the literature, only a few studies have reported the parental mental illness associated with retinoblastoma in their child [14, 26–29]. Moreover, there are no studies from India or Asia on psychological illness in the parents of retinoblastoma

patients. Also, studies on the impact of YBLI on improving mental health and QOL as well as impact on cardinal biomarkers of neuroplasticity and mind-body communicative biomarkers in the parents of retinoblastoma patients are lacking. YBLI enables optimized response to physical and psychological stresses by appropriately regulating the cognitive, emotional, and behavioural output, accompanied by optimum autonomic output, physical strength, flexibility and vitality, healthy inflammatory response, healthy diet and sleep patterns. All these mentioned cognitive and behavioural outputs of YBLI are mediated through its control on parasympathetic nervous system. BDNF is a cardinal biomarker of neuroplasticity and plays an important role in neurogenesis. Naveen et al. reported increased serum BDNF levels followed by 3 months of YBLI practice in patients with MDD [47]. In our study, we have also found increased BDNF levels along with improvement in mind-body communicative biomarkers post-YBLI and thus, improvement in psychological stress symptoms and overall QOL in the participants. DHEAS is a sex steroid precursor. It easily crosses the blood-brain barrier and in the central nervous system, it has neuroprotective functions and possesses properties such as anti-inflammatory, pro-survival and anti-glucocorticoid [48]. Increased levels of DHEAS are associated with decline in depressive symptoms in patients with MDD by reducing the brain excitability [49]. DHEAS negatively affects the synthesis of IL-6 which is a major cytokine involve in neuroinflammation [50, 51]. In our study we have found significant increase in DHEAS and decline in IL-6 levels followed by YBLI. From this we may conclude that decline in the depressive symptoms in the participants followed by YBLI is mediated through elevated levels of DHEAS which in turn decrease the IL-6 and increases BDNF which activates them-TOR pathway and thus, mediates the neuroprotective role and synaptic plasticity [52]. Sirtuin 1 (a histone deacetylase) located in the nucleus is involved in nutritional and energy sensing pathways. It forms an auto-regulatory feedback loop and regulates the reactive oxygen species levels and thus, promotes cellular longevity [53]. It also prevents neuronal cell death, regulates oxidative stress levels and promotes synaptic

plasticity [54]. In our study, we have found increased sirtuin 1 levels post-YBLI. Increased cortisol levels are an indicative of stress responsiveness and leads to increased neurodegeneration [55]. Studies have also reported that sustained stress leads to elevated cortisol levels which suppresses BDNF secretion in the brain via suppressing the glucocorticoid receptors which further decline synaptic plasticity and hence, leads to neurodegeneration [56]. In our study, decreased cortisol levels were found post-YBLI in the parents of retinoblastoma patients. The findings of our study implies significant improvement in biomarkers of neuronal plasticity {cardinal biomarker of neuroplasticity (BDNF)} and mind-body communicative biomarkers (DHEAS, sirtuin1, cortisol and IL-6) in association with the positive clinical outcomes i.e., reduction in depressive symptoms in the parents of retinoblastoma patients along with overall improvement in QOL. This suggests that YBLI acts not only at the physical level but also at the level of brain, mind-body communication as well as cellular health and may serve as an essential adjunctive therapy in clinical settings to provide standard of care not only to the cancer patients but also to their caregivers as it improves overall health and help the caregivers to cope up with psychological stress burden associated with cancer treatment.

In most of the sporadic heritable retinoblastoma patients, the constitutional mutation (i.e., first hit in the *RB1* gene) mainly occurs as a *de novo* paternal germ line mutation which may occur during spermatogenesis [57]. In a previously published study from our lab, we have documented that cigarette smoking and tobacco chewing/smoking is associated with seminal oxidative stress and oxidative DNA damage that may contribute to the development of childhood cancers due to accumulation of 8 hydroxy 2 deoxyguanosine which induces mutations and epimutations [24]. Another study from our lab has reported decline in seminal oxidative stress and oxidative DNA damage and decrease in 8hydroxy2deoxyguanosine levels in the fathers of retinoblastoma patients followed by six months of YBLI practice. There was a significant decline in oxidative stress markers such as reactive oxygen species, DNA fragmentation index and 8-hydroxy-2'-deoxyguanosine post-YBLI. This study suggested that oxidative stress induced sperm DNA damage as a result of mutagenic base adduct formation, genomic hyper mutability, aberrant sperm methylation patterns could be prevented by adoption of YBLI [22]. This can prevent cancer in the individual and in the next generation both by genetic and epigenetic mechanisms [22]. This mechanism of action of yoga is mediated through the regulation of hypothalamic-pituitary-gonadal (HPG) and hypothalamopituitary adrenal (HPA) axis [58]. Yoga regulates neuro-hormonal mechanisms that reduces stress and anxiety, regulates autonomic functions and thus, improves the reproductive health and psychological health and thus has preventive, promotive, curative and rehabilitative potential.

Limitation of the study

One limitation of the study is the small sample size. At the end of the intervention (after 12 weeks) most of the participants

were very satisfied with the YBLI and none of them showed any negative perception regarding the intervention.

Conclusion

YBLI improves overall health and QOL and reduces psychological stress experienced by the parents of retinoblastoma patients. It also reduces the severity of depression experienced by the parents of these patients by improving the biomarkers of neuronal plasticity. YBLI is an essential therapy for management of psychological stress for the parental caregivers of retinoblastoma patients.

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Authorship contribution

Contributor SB has recruited the patients, collected the data and written the final manuscript. RD and MT supervised the statistical analysis. MT helped in screening patients and collecting the data. RD and BC helped in developing the concept and designing the protocol and corrected the manuscript to the final version. RM provided yoga training.

Ethical statement

The study was initiated after approval from Institute's Ethics Committee (ESC/T-370/22-07-2015) and after obtaining registration of the clinical trial; Clinical Trial Registry of India (CTRI) REF/2014/09/007532.

Source of funding

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Conflict of interest

The authors declare no competing or financial interests.

ICMJE Guidelines-The manuscript complies with International Committee of Medical Journal Editors (ICMJE) guidelines.

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Abbreviations

BDI-II	Beck depression inventory-II
BDNF	Brain derived neurotrophic factor
CTRI	Clinical Trial Registry of India
DHEAS	Dehydroepiandrosterone sulphate

DSM-V	Diagnostic and Statistical Manual for Mental Disorder-V
ELISA	Enzyme-linked immunosorbent assay
HPA axis	Hypothalamo-pituitary-adrenal axis
HPG axis	Hypothalamic-pituitary-gonadal axis
IL-6	Interleukin-6
MDD	Major depressive disorder
QOL	Quality of life
WHOQOL-BREF	World health organisation quality of life-BREF
YBLI	Yoga based lifestyle intervention

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