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

Shilpa Bishta, Bhavna Chawla, Madhuri Tolahunase, Richa Mishra, Rima Dada

*Laboratory for Molecular Reproduction and Genetics, Department of Anatomy, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.

Ocular Oncology Service, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.

ANNALS OF NEUROSCIENCES
VOLUME 26 NUMBER 2 APRIL 2019 www.annalsofneurosciences.org

**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.

doi 10.5214/ans.0972.7531.260206

**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 late, 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 regarding 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 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.

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.

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

| Session                                                                 | Duration |
|------------------------------------------------------------------------|----------|
| 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-Shavasana                                                        | 2 min    |
| Uttanpadasana                                                           | 2 min    |
| Pawanmuktasana                                                         | 2 min    |
| Setubandhasana                                                          | 2 min    |
| Prone-Mala rasana                                                       | 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                                                              |          |
| Bhastrika                                                               |          |
| Ujjayi                                                                  | 35 min   |
| 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  |

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.

---

**Note:**

- **QOL (domain scores are scaled in a positive direction):**
- **WHOLQO: A 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).**
Secondary outcomes
The secondary outcome included pre-and-post evaluation of blood biomarkers of neuroplasticity which included: the card-inal 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 vi-als and was centrifuged at 2000 g for 15 minutes at 4°C. Both serum and plasma were stored at -80°C until analysed. The biomarkers were estimated using commercially avail-able enzyme-linked immunosorbent assay (ELISA) kits for esti-mating the levels of BDNF (Raybiotech, Inc), sirtuin 1 (Qayee Bio-Technology), DHEAS (Qayee Bio-Technology), cortisol (DRG Diagnostic, Germany), and IL-6 (Gen-Probe, Diadome 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 with- in 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. The 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<.0001) (figure 2).

WHOQOL-BREF questionnaire was also assessed in the participants at day 0 and after 12-weeks of YBLI. The partic-ipants 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
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

### Socio-demographic characteristics

| 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)                  |

**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).
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

| 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   | 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 |

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

**Acknowledgment**

The authors would like to thankfully acknowledge all the parents of retinoblastoma patients who took part in the study. We would also like to pay sincere thanks to our yoga instructor: Mrs. Richa Mishra.

**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**

The funding for the study was provided by Indian Council of Medical Research (Grant No. ICMR-1930) and Ministry of Ayush (Grant No. N-1737). Financial assistance by the Council of Scientific & Industrial Research (Human Resource Development Group), New Delhi, India, in the form of a Senior Research Fellowship to Ms. Shilpa Bisht is thankfully acknowledged.

**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.

**Received Date**: 27-05-19; **Revised Date**: 01-08-19; **Accepted Date**: 04-08-19

**Abbreviations**

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

World health organization quality of life-BREF

YBLI
Yoga based lifestyle intervention

References

1. Lindahl Norberg A, Boman KK. Parent distress in childhood cancer: A comparative evaluation of posttraumatic stress symptoms, depression and anxiety. Acta Oncologica. 2008;47 (2):267–74.

2. Nijboer C, Templeaar R, Sanderman R, Triemstra M, Spruijt RJ, Van Den Bos GA. Cancer and caregiving; the impact on the caregiver’s health. Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer. 1998;7 (1):3–13.

3. Carter PA, Chang BL. Sleep and depression in cancer caregivers. Cancer nursing. 2000;23 (6):410–5.

4. Rha SY, Park Y, Song SK, Lee CE, Lee J. Caregiving burden and the quality of life of family caregivers of cancer patients: the relationship and correlates. European Journal of Oncology Nursing, 2015;19 (4):376–82.

5. Group W. The World Health Organization quality of life assessment (WHO-QOL): position paper from the World Health Organization. Social science & medicine. 1995;41 (10):1403–9.

6. Wiener L, Viola A, Kearney J, Mullins LL, Sherman-Bien S, Zadeh S, et al. Impact of caregiving for a child with cancer on parental health behavior, relationship quality, and spiritual faith: do lone parents fare worse? Journal of Pediatric Oncology Nursing. 2016;33 (5):378–86.

7. Okado Y, Long AM, Phipps S. Association between parent and child distress and the moderating effects of life events in families with and without a history of pediatric cancer. Journal of pediatric psychology. 2014;39 (9):1049–60.

8. Schepers SA, Sint Nicolaas SM, Maurice-Stam H, Haverman L, Verhaak CM, Bos GA. Cancer and caregiving: the impact on the caregiver’s health. Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer. 1998;7 (1):3–13.

9. Shields CL, Shields JA. Diagnosis and management of retinoblastoma. Cancer control. 2004;11 (5):317–27.

10. Dimaras H, Kimani K, Dimba EA, Grondahl P, White A, Chan HS, et al. Retinoblastoma. The Lancet. 2012;379 (9824):1436–46.

11. Knudson AG. Mutation and cancer: statistical study of retinoblastoma. Proceedings of the National Academy of Sciences. 1971;68 (8):2820–3.

12. Chawla B, Hasan F, Azad R, Seth R, Upadhyay BD, Parthy S, et al. Clinical presentation and survival of retinoblastoma in Indian children. British Journal of Ophthalmology. 2016;100 (2):172–8.

13. Chawla B, Kumar K, Singh AB. Influence of socioeconomic and cultural factors on retinoblastoma management. Asia-Pacific journal of oncology nursing. 2017;4 (3):187.

14. Wilard VV, Qaddumi I, Zhang H, Huang L, Russell KM, Brennan R, et al. A longitudinal investigation of parenting stress in caregivers of children with retinoblastoma. Pediatric blood & cancer. 2017;64 (4):e26279.

15. Pai AL, Greenley RN, Lewandowski A, Drotar D, Youngstrom E, Peterson CC. A meta-analytic review of the influence of pediatric cancer on parent and family functioning. Journal of Family Psychology. 2007;21 (3):407.

16. Yadav RK, Magan D, Mehta N, Sharma R, Mahapatra SC. Efficacy of a short-term yoga-based lifestyle intervention in reducing stress and inflammation: preliminary results. The journal of alternative and complementary medicine. 2012;18 (7):662–7.

17. Cahn BR, Goodwin MS, Peterson CT, Maturi R, Mills PJ. Yoga, meditation and mind-body health: increased BDNF, cortisol awakening response, and altered inflammatory marker expression after a 3-month yoga and meditation retreat. Frontiers in human neuroscience. 2017;11:315.

18. Goldberg SR, Tucker RP, Greene PA, Davidson RJ, Wampold BE, Kearney DJ, et al. Mindfulness-based interventions for psychiatric disorders: A systematic review and meta-analysis. Clinical psychology review. 2018;59:52–60.

19. Prathikanti S, Rivera R, Cochran A, Tungel JG, Fayzazmehne N, Weinmann E. Treating major depression with yoga: A prospective, randomized, controlled pilot trial. Plos one. 2017;12 (3):e0173869.

20. Tolahunase MR, Sagar R, Faq M, Dada R. Yoga-and meditation-based lifestyle intervention increases neuroplasticity and reduces severity of major depressive disorder: A randomized controlled trial. Restorative neuroscience and neurocience. 2018 (Preprint):1–20.

21. Gautham S, Chawla B, Bishit S, Tolahunase M, Dada R. Impact of mindfulness based stress reduction on sperm DNA damage. Journal of the Anatomical Society of India. 2018;67 (2):124–9.

22. Dada R, Kumar SB, Chawla B, Bishit S, Khan S. Oxidative Stress Induced Damage to Paternal Genome and Impact of Meditation and Yoga Can Reduce Incidence of Childhood Cancer? Asian Pacific Journal of Cancer Prevention. 2016;17 (9):4517–25.

23. Kumar SB, Chawla B, Bishit S, Yadav RK, Dada R. Tobacco use increases oxidative DNA damage in sperm-potential etiology of childhood cancer. Asian Pac J Cancer Prev. 2015;16 (16):6967–72.

24. Hölzel BK, Carmody J, Vangel M, Congleton CM, Yerramsetti SM, Gard T, et al. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Research: Neuroimaging. 2011;191 (1):36–43.

25. Eyre HA, Acevedo R, Yang H, Siddarth P, Van Dyk K, Ercoli L, et al. Changes in neural connectivity and memory following a yoga intervention for older adults: a pilot study. Journal of Alzheimer’s Disease. 2016;52 (2):673–84.

26. Ek U. Emotional reactions in parents and children after diagnosis and treatment of a malignant tumour in the eye. Child: care, health and development. 2000;26 (5):415–28.

27. Hamama-Raz Y, Toju K, Suzuki S, Okamitsu M, Omori T. Parenting stress related to raising infants receiving treatment for retinoblastoma-malignant eye cancer. Journal of psychosocial oncology. 2012;30 (1):21–40.

28. Nagayoshi M, Hirose T, Toju K, Suzuki S, Okamitsu M, Omori T. Parenting stress related to raising infants receiving treatment for retinoblastoma. Psycho-oncology. 2016;25 (12):1507–11.

29. Tröster H. Sources of stress in mothers of young children with visual impairments. Journal of Visual Impairment & Blindness (JVIB). 2001;95 (10).

30. Arora R, Eden T, Kapoor G. Epidemiology of childhood cancer in India. Indian journal of cancer. 2009;46 (4):264.

31. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.

32. Beck AT, Ward C, Mendelson M, Mock J, Erbaugh J. Beck depression inventory (BDI). Arch Gen Psychiatry. 1961;4 (6):561–7.

33. Basker M, Moses PD, Russell S, Russell PSS. The psychometric properties of Beck Depression Inventory for adolescent depression in a cultural groups worldwide. Health psychology. 1999;18 (5):495.

34. Beck AT, Steer RA, Brown GK. Beck depression inventory-II. San Antonio. 1996;78 (2):490–8.

35. Saxena S, Orley J, Group W. Quality of life assessment: the World Health Organization perspective. European psychiatry. 1997;12:263s–6s.

36. Power M, Bullinger M, Harper A. The World Health Organization WHOQOL-100: Tests of the universality of quality of life in 15 different cultural groups worldwide. Health psychology. 1999;18 (5):495.

37. Batra P, Kumar B, Gomber S, Bhatia M. Assessment of quality of life during treatment of pediatric oncology patients. Indian journal of public health. 2014;58 (3):168.
38. Klassen AF, Raina P, McIntosh C, Sung L, Klaassen R, O’Donnell M, et al. Parents of children with cancer: Which factors explain differences in health-related quality of life. International Journal of Cancer. 2011;129 (5):1190–8.

39. Dahlquist LM, Czyzewski DI, Copeland KG, Jones CL, Taub E, Vaughan JK. Parents of children newly diagnosed with cancer: anxiety, coping, and marital distress. Journal of pediatric psychology. 1993;18 (3):365–76.

40. Sawyer MG, Steiner DL, Antoniou G, Tongood I, Rice M. Influence of parental and family adjustment on the later psychological adjustment of children treated for cancer. Journal of the American Academy of Child & Adolescent Psychiatry. 1998;37 (8):815–22.

41. Litelzelman K, Catrine K, Gangnon R, Witt WP. Quality of life among parents of children with cancer or brain tumors: the impact of child characteristics and parental psychosocial factors. Quality of life Research. 2011;20 (8):1261–9.

42. Visser A, Huizinga GA, van der Graaf WT, Hoekstra HJ, Hoekstra-Weebers JE. The impact of parental cancer on children and the family: a review of the literature. Cancer treatment reviews. 2004;30 (8):683–94.

43. Singh VP, Khandelwal B, Sherpa NT. Psycho-neuro-endocrine-immune mechanisms of action of yoga in type II diabetes. Ancient science of life. 2015;35 (1):12.

44. Khalsa SBS. Yoga for psychiatry and mental health: an ancient practice with modern relevance. Indian journal of psychiatry. 2013;55 (Suppl 3):S334.

45. Froeliger B, Garland EL, Modlin LA, McClernon FJ. Neurocognitive correlates of the effects of yoga meditation practice on emotion and cognition: a pilot study. Frontiers in integrative neuroscience. 2012;6:48.

46. Desai R, Tailor A, Bhatt T. Effects of yoga on brain waves and structural activation: A review. Complementary therapies in clinical practice. 2015;21 (2):112–8.

47. Naveen G, Varambally S, Thirthalli J, Rao M, Christopher R, Gangadhar B. Serum cortisol and BDNF in patients with major depression—effect of yoga. International review of psychiatry. 2016;28 (3):273–8.

48. Stoffel-Wagner B. Neurosteroid metabolism in the human brain. European Journal of Endocrinology. 2001;145 (6):669–80.

49. Pennisi M, Lanza G, Cantone M, Ricceri R, Spampinato C, Pennisi G, et al. Correlation between motor cortex excitability changes and cognitive impairment in vascular depression: pathophysiological insights from a longitudinal TMS study. Neural plasticity. 2016;2016.

50. Erta M, Quintana A, Hidalgo J. Interleukin-6, a major cytokine in the central nervous system. International journal of biological sciences. 2012;8 (9):1254.

51. Straub R, Koncic L, Krutz S, Rothe G, Kreutz M, Scholmerich J, et al. Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin-6 (IL-6), and DHEA inhibits IL-6 secretion from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence. The Journal of Clinical Endocrinology & Metabolism. 1998;83 (6):2012–7.

52. Chen A, Xiong L-J, Tong Y, Mao M. Neuroprotective effect of brain-derived neurotrophic factor mediated by autophagy through the PI3K/Akt/mTOR pathway. Molecular medicine reports. 2013;8 (4):1011–6.

53. Michan S, Sinclair D. Sirtuins in mammals: insights into their biological function. Biochemical Journal. 2007;404 (1):1–13.

54. Singh P, Hanson PS, Morris CM. SIRT1 ameliorates oxidative stress induced neural cell death and is down-regulated in Parkinson’s disease. BMC neuroscience. 2017;18 (1):46.

55. Widmer IE, Puder JJ, König C, Pargger H, Zerkowski HR, Girard Jr, et al. Cortisol response in relation to the severity of stress and illness. The Journal of Clinical Endocrinology & Metabolism. 2005;90 (8):4579–86.

56. Chen H, Lombès M, Le Menuet D. Glucocorticoid receptor represses brain-derived neurotrophic factor expression in neuron-like cells. Molecular brain. 2017;10 (1):12.

57. Zhu X, Dunn JM, Phillips RA, Goddard AD, Paton KE, Backer A, et al. Preferential germline mutation of the paternal allele in retinoblastoma. Nature. 1989;340 (6231):312.

58. Sengupta P, Chaudhuri P, Bhattacharya K. Male reproductive health and yoga. International journal of yoga. 2013;6 (2):87.