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Evaluation of management of Stress in Cancer Patients through *Shirodhara* w.s.r. to Cancer Metastasis and Stress Hormones - A Review

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ABSTRACT

The psychosocial factors on the development and progression of cancer have been a longstanding hypothesis since ancient times. In fact, epidemiological and clinical studies over past 30 years have provided strong evidence for links between chronic stress, depression, social isolation and cancer progression. By contrast, there is only limited intervention for managing behavioral factors in cancer progression. The major cause of death in cancer is metastasis that is resistant to conventional therapy. The outcome of cancer metastasis depends on multiple interactions between metastatic cells and homeostatic environment of the body. Epinephrine Norepinephrine Cortisol Catecholamine's are known to be elevated in individuals with stress. The physiological stress response is thought to be one of the likely mediators in cancer progression, Hypothalamic Pituitary Adrenal (HPA) axis is considered to be the main neurophysiological mechanism of *Shirodhara*, the tactile stimulation of skin or hair follicles innervated by Trigeminal cranial nerve stimulate the thalamus and provide the subject an altered state of consciousness and a relief from anxiety, stress and depression. Other route from the principal nucleus to the reticular formation and posterior region of thalamus, which is Centre of autonomic nervous system, would be possible. This provides changes in autonomic nervous balance, *Shirodhara* can be treated as a good option to prevent stress and maintain homeostasis.

Key words: Homeostasis, Metastasis, *Shirodhara*, Hypothalamus Pituitary Adrenal axis.

INTRODUCTION

Each year, the American Cancer Society estimates the numbers of new cancer cases and death and compiles the most recent data on cancer incidence, mortality, and survival. In 2019, 1,762,450 new cancer cases and 606,880 cancer deaths are projected to occur in the United States.^[1] The overall cancer death rate

dropped continuously from 1991 to 2016 by a total of 27%, translating into approximately 2,629,200 fewer cancer deaths than would have been expected if death rates had remained at their peak. Although cancer mortality rate is slowly narrowing, socioeconomic inequalities are widening, with the most notable gaps for the most preventable cancers. For example, compared with the most affluent counties, mortality rates in the poorest counties were 2-fold higher for cervical cancer and 40% higher for male lung and liver cancers during 2012-2016. A broader application, awareness, advanced diagnostics; prevention of existing cancer would undoubtedly accelerate progress against cancer.

Stress and Cancer - There has been a strong correlation of the influence of psychosocial factors on the development and progression of cancer, In fact, epidemiological and clinical studies over the past 30 years have provided strong evidence for links

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between chronic stress, depression and social isolation and cancer progression.^[2] Recent cellular and molecular studies have identified relationship between psychosocial factors, specifically chronic stress, and cancer progression. Stress is a complex process including environmental and psychosocial factors that initiate a cascade of information processing in both the peripheral nervous system and CNS^[3] Stress can be acute (short-lived) or chronic (repetitive or occurring over an extended period of time). Under chronic stress conditions, the body remains in a constant state of 'overdrive', with deleterious downstream effects on regulation of stress response systems, as well as many organ systems^[4] Both norepinephrine (NE) and epinephrine (E) are known to be elevated in individuals with acute or chronic stress.^[5] Furthermore, dopamine (DA) levels are increased in the brain during acute stress. However, under chronic stress; DA levels are lower as a consequence of decreased release of DA. A variety of stressors, including severe trauma, marital discord and bereavement, as well as depression and social isolation, have been associated with deregulation or alterations in various neuroendocrine hormones, particularly catecholamine's and cortisol.^[6] Stress response involves activation of several body systems including the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. The 'fight or flight' response is elicited by the production of mediators such as NE and E from the sympathetic nervous system (SNS) and the adrenal medulla. The HPA response includes release of corticotrophin - releasing hormone from the hypothalamus, which induces secretion of adrenocorticotrophic hormone from the anterior pituitary, resulting in downstream release of glucocorticoids (GCs) such as cortisol from the adrenal cortex.^[7]

Metastasis is a complex process that requires several steps to be successful, including angiogenesis, proliferation, invasion, embolization and evasion of immune system surveillance. Growth of a tumor beyond 1 mm in size requires vascularization of the tumor, which also provides a method for dissemination of metastatic cells.^[8] Moreover, a

tumor cell must gain the ability to break off from the main tumor, invade through the basement membrane and embolize into the bloodstream. The cell then arrests in capillary beds and must be able to extravagate from the bloodstream and adhere to parenchymal tissues. Once settled, the metastatic cell interacts with its new microenvironment to grow and ultimately develop its own blood supply. Increasing evidence shows that the stress response can affect many parts of this cascade.^[9] Additional neuroendocrine factors are also modulated following stress, including DA, prolactin, NGF, substance P and oxytocin.^[10]

Alternative healing since ages had wrote about *Panchakarma* therapeutic process i.e. *Shirodhara*.^[11] *Shirodhara* is deeply relaxing and induces a relaxant state; the center of the forehead, where *Shirodhara* is being done is evolution wise related to the third eye, and is connected to the pineal gland. This spot is known as *Agnya Chakra* in the *Yoga* tradition. Focusing on *Agnya Chakra* with closed eyes during meditation leads to psychosomatic harmony. As the oil drips on the *Agnya Chakra*, it is proposed that the meditation-like effect is a consequence of stillness of mind leading to adaptive response to stress. *Shirodhara* is widely practiced in *Ayurveda* and is usually indicated to treat stress, anxiety, and insomnia and to relax the nervous system.^[12] Varied research work has been conducted to visualize the effect of *Shirodhara* on ECG, EEG, Stress hormones, hypothalamus pituitary adrenal complex.

METHODOLOGY

Electronic databases were searched from 1946 to present, Database of Systematic Reviews - 2005 to January 2015, Searches were also run in PubMed. Google was used to search for additional web-based materials and information. No limits were applied. Additional articles were identified from reviewing the references of retrieved articles. The purpose of this study is to review papers of different authors associated with stress and *Shirodhara* and aims to develop conceptual framework, existing gaps and future research direction for further advancement,

and bring out the preventive, supportive, rehabilitative aspect of *Shirodhara* in cancer management.

- 1) *Shirodhara*: A psycho-physiological profile in healthy volunteers by Kalpana D. Dhuri, Prashant V. Bodhe, Ashok B. Vaidya Department of Clinical Research, ICMR ^[13]

The study was conducted in the human pharmacology laboratory. The study design was open labeled, comparing the baseline variables with values after *Shirodhara*. The subjects (n = 16) chosen were healthy human volunteers. *Shirodhara* was preceded by *Abhyanga* – whole body massage. The *Shirodhara* method was standardized for rate of dripping with peristaltic pump and temperature was controlled with a thermostat. Mood and stress levels were assessed by validated rating scales. The pre- and post – *Shirodhara* baseline temperature, BP, Heart Rate, ECG, and salivary cortisol and urinary catecholamine's were collected.

Student's paired "t" test was applied to the means + SE of the variables to calculate statistical significance at P < 0.05. There was a significant improvement in mood scores and the level of stress (P < 0.001). After *Shirodhara*, volunteers showed a significant (P = 0.002) reduction in the respiratory rate. The mean diastolic blood pressure also reduced significantly (P = 0.027), with a significant (P = 0.0015) drop in the mean pulse rate. ECG confirmed the heart rate reduction, with no other changes in the atrial or ventricular complexes. In all the 16 subjects, EEG showed an increase in the Alfa rhythm after *Shirodhara*. The EEG changes are similar to those observed after deep meditation and alert relaxation. The V.A.S. score and M.A.S. score for stress and mood changed significantly (P = 0.003). The mean value of salivary cortisol post - *Shirodhara* was not significantly different (P = 0.58) from that of the pre *Shirodhara* value. However, the individual values showed a decreasing trend. The means of pre- and post - *Shirodhara* urinary Creatinine levels did not differ significantly (P = 0.46). The means of pre - and post - *Shirodhara* urinary epinephrine levels were not

significantly different from each other (P = 0.62), as also the means of pre - and post *Shirodhara* urinary norepinephrine levels that were not significantly different from each other (P = 0.39).

- 2) Clinical efficacies of *Manasamitra Vataka* and *Shirodhara* over clonazepam in preserving slow wave sleep and promote sleep continuity in patients with generalized anxiety disorder by Basavaraj R. Tubaki et.al.^[14]

This study show potential of Ayurvedic interventions i.e. *Shirodhara* as a treatment of choice in the management of anxiety disorders.

This was an open labeled, controlled, parallel and randomized study conducted at NIMHANS, Bangalore. A total of 72 patients were taken and were randomized (blocked randomization) into one of the three groups; Group-I, (n = 24) received tablet *Manasamitra Vataka* (100 mg, twice daily, for 30 days according to the literature), group-II (n = 24) received *Shirodhara* with *Brahmi Tailam* (oil-based extract of *Bacopa monniera*) in the morning for the first seven days in addition to tablet *Manasamitra Vataka* as mentioned for group-I. Group-III (n = 24) received clonazepam tablet (0.25 mg in the morning and 0.50 mg at night) for 30 days.

Whole night polysomnography was carried out to assess the sleep architecture and spindle – delta dynamics. Sleep quality and duration of night awakenings which was improved in group-II (P = 0.005) and group-III (P = 0.006) as compared to group-I (P=0.015).

This study highlights the sleep promoting and preserving nature of *Manasamitra Vataka* and *Shirodhara* in GAD patient over clonazepam. *Shirodhara* treatment had an add-on effect on *Manasamitra Vataka* treatment, as it helped improve the sleep continuity by reducing the micro-arousals and also the daytime sleepiness.

- 3) Effects of *Ayurvedic* Oil-Dripping Treatment with Sesame Oil vs. with Warm Water in improving sleep quality index by Akiko Tokinobu et.al.^[15]

This study aimed to quantitatively evaluate the effect of sesame oil *Shirodhara* (SOS) against warm water *Shirodhara* (WWS) on improving sleep quality and quality of life (QOL) among persons reporting sleep problems. This randomized, single-blinded, crossover study recruited 20 participants. Each participant received seven 30-minute sessions within 2 weeks with either liquid. The washout period was at least 2 months. The *Shirodhara* procedure was conducted by a robotic oil-drip system. The outcomes were assessed by the Pittsburgh Sleep Quality Index (PSQI) for sleep quality, Epworth Sleepiness Scale (ESS) for daytime sleepiness, World Health Organization Quality of Life 26 (WHO-QOL26) for QOL, and a sleep monitor instrument for objective sleep measures.

Results: Out of 20 participants, 15 completed the study. SOS improved sleep quality, as measured by PSQI. The SOS score was 1.83 points lower (95% confidence interval [CI], -3.37 to -0.30) at 2-week follow-up and 1.73 points lower (95% CI, -3.84 to 0.38) than WWS at 6-week follow-up. Although marginally significant, SOS also improved QOL by 0.22 points at 2-week follow-up and 0.19 points at 6-week follow-up compared with WWS.

4) Psycho-neuroimmunologic effects of Ayurvedic Oil-Dripping Treatment by Kazuo Uebaba et.al.^[16]

This study assessed the psychoneuroimmunologic changes achieved by *Shirodhara* using a robotic system. In this 16 healthy females underwent a 30-minute treatment in supine position for 30 minutes, with monitoring of physiologic, biochemical, immunologic, and psychometric parameters including anxiety and altered states of consciousness (ASC).

The subjects who received *Shirodhara* treatment showed lowered levels of state anxiety and higher levels of ASC. Plasma noradrenaline and urinary serotonin excretion decreased significantly more after *Shirodhara* treatment than in the control. Plasma levels of thyrotropin-releasing hormone, dopamine, and natural killer (NK) cell activity were different between control and *Shirodhara* treatment. The correlation between anxiolysis and the depth of ASC was significant in the *Shirodhara* treatment group

($r=0.52$, $p=0.05$, $N=16$), while in the control no correlation was obtained ($r=0.13$, $p=0.64$, $N=16$).

These results indicate that *Shirodhara* has anxiolytic and ASC-inducing effects, and it promotes a decrease of noradrenaline and exhibits a sympatholytic effect.

5) Using a Healing Robot for the Scientific Study of *Shirodhara* treatment by Kazuo uebeba^[17]

Anxiolytic effects of *Shirodhara* in the subjects with High Anxiety of the 57 subjects, (>40) had successive *Shirodhara* treatments four times every week. The changes in the POMS score were assessed after the final *Shirodhara*. The result indicated a significant decrease of tension and anxiety (Wilcoxon signed rank test, $p < 0.05$) and a tendency towards a decrease in exhaustion. Concerning the other domains, the trend for the average level with *Shirodhara* showed improvement, but none of these differences were statistically significant. Anxiolytic Effects of the *Shirodhara* At first, STAI scores of 12 healthy female subjects by *Shirodhara* were compared with those of 12 other subjects who had algae packs applied facially for relaxation. The subject's state of anxiety, assessed just before and after *Shirodhara*, decreased abruptly ($p < 0.005$, Wilcoxon signed rank test), while the decrease in anxiety in subjects receiving the algae pack was not as large as *shirodhara* ($p < 0.05$).

6) Singhal HK, N, Kumar A, Rai M. Ayurvedic approach for improving reaction time of attention deficit hyperactivity disorder affected children by Singhal hk, Kumar A , Rai M^[18]

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood. Singhal et al.(2010) conducted investigation to evaluate the increase in attention span in 43 ADHD-affected children treated with different *Ayurvedic* approaches. In their study, selected children of both sexes in the age-group of 6–16 years were divided into three groups. In group A, 17 patients received syrup *Ayurvedic* compound I (*Bacopa monnieri* Linn – 42.86%, *Withania somnifera* Linn – 28.57%, *Valerian walichi* DC – 28.57%); in group B, 14 patients were treated with syrup *Ayurvedic* compound I + *Shirodhara* with milk; and in group C, 12

patients received placebo syrup. The dose of the drug was 1.0 ml/kg body weight and the duration of treatment was 3 months. It was observed that Group B showed highly significant ($P < .001$) improvement in total reaction time, while in group C the change was statistically nonsignificant $P > 0.10$. Further, it was observed that the drug and *Shirodhara* were both effective in improving the reaction time of ADHD affected children, but the drug combined with *Shirodhara* was superior to the drug used alone.

7) An assessment of *Manasika Bhavas* in menopausal syndrome and its management by Santwani K, Shukla V D, Santwani M A, Thaker G^[19]

Psychological symptoms of Menopause Women experience range psychological symptoms irritability, lack of concentration, mood swings, depressive mood etc. Santwani et al.(2010) conducted a clinical trial to evaluate the efficacy of *Shirodhara* and *Saraswatarishta* as compared to hormone replacement therapy (HRT) in the management of menopausal syndrome, along with the assessment of *Manasika Bhavas*. The subjects were randomly divided into three groups i.e. Group A, Group B and Group C. Total 48 patients were selected for the study, out of which 43 patients completed the study. Group A patients were treated with conjugated estrogens 0.625 mg once daily for 45 days. Group B was treated with *Saraswatarishta* 20 ml mixed with water and taken before meals twice a day for duration of 45 days and in Group C *Shirodhara* with *Bala Taila* was administered, 30 min per sitting for 45 days. Specialized Ayurvedic rating scales like *Manasa Pariksha Bhavas* as well as the Hamilton Anxiety Rating Scale, Hamilton Depression Rating scale, and Menopause Rating Scale were adopted to assess the effect of therapy.

It was observed that Patients undergoing *Shirodhara* had better relief of the disturbances of *Manasa Bhavas* and psychic symptoms of menopause as compared to the other two groups. Group C showed highly significant result ($< .001$) in *Moha*, *Shoka*, *Bhaya*, *Medha* and *Smriti*, whereas there was

insignificant result in *Krodha* ($P > .01$). Group A showed relief in psychic symptoms of menopause, but the change was statistically nonsignificant ($P < = .10$). Group B and Group C showed highly significant result ($P < + .001$) in all the psychic symptoms of menopause.

Group A there was highly significant relief ($P < = .001$) of all the somatic symptoms, except constipation, flatulence, backache, joint pain. Group B showed significant highly significant results ($P < = .001$) in somatic symptoms of menopause. Group C shows highly significant result ($P < = .001$) in all somatic symptoms.

Group A showed highly significant results ($P < = .001$) in all symptoms assessed by Hamiltons Depression Rating Scale. Group B and C showed highly significant result ($P < = .001$) except in cases of Psychomotor retardation.

RESULT & ANALYSIS

With a detailed study of the above articles it can be clearly stated that continuous pouring of liquid on forehead for a specific period has Tranquilizing effect and induces Sleep. Above Dhuri et.al. 2019 Shows its effect on hypothalamic – pituitary-adrenal axis, it has Alpha Adrenergic blocking effect and can thus block certain actions of adrenaline and nor adrenaline. *Shirodhara* may also reduce the synthesis of noradrenaline. As hypothalamus is the main controller of endocrine secretions. The hypothalamic Neurons which secrete the regulatory hormones are themselves under the control of specialized monoaminergic, neurotransmitter neurons which arise in the mid brain. These latter release Dopamine, Nor-adrenaline and Serotonin. In turn, these mid brain nuclei are under the control of visceral brain and are responsive to stress and emotional disturbances. Regulation of emotional and behavioral patterns together with the limbic system and the hypothalamus regulates the feeling of rage, aggression, pain, pleasure and behavioural patterns of sexual arousal. Stated by Basavaraj R Tubaki et.al. It can be postulated that *Shirodhara* may be having some effect on hypothalamus resulting in decrease of

most of the psychic and somatic disorders. Almost all the subjects in the above mentioned works who have received *Shirodhara* treatment showed a reduction in their anxiety levels as per the mood assessment scores. Changes in vital signs like Blood Pressure, Heart Rate, EEG, ECG, salivary cortisol, and urinary catecholamines were also seen which as putative correlates of stress. Three studies reported that as anxiety scores decrease, the ASC scores increase and the skin temperature of the foot increases with increased in ASC scores and decreased in anxiety scores. All the above studies showed significant result in the subjective criteria pre and post *Shirodhara* i.e. Hamilton Anxiety Scale, Appesworth Scale, PSQI Pittsburgh Sleep Quality Index, *Mansika Bhavas*, Visual Analogue Scale, Mental Analogue Scale but there was also a quite significant data in objective criteria i.e. ECG, EEG, Cortisol, Adrenaline, Nonadrenaline, Creatine, Sleep Dynamics. The statistical significance of Dhuri et.al. 2019 due to very small sample size was though not significant in saliva cortisol but it showed a much lower value post *Shirodhara*. Basavraj.et.al. did the work with a good sample size and significant result but was added with *Manasmitravatak* showing it as a supportive therapy in anxiety disorder.

Robotic *Shirodhara* by Kazuo Uebaba postulated anxiolytic effect of *Shirodhara*, with a decrease in STAI (State Trait Anxiety Inventory) and POMS (Profile of Mood State), it could have been advanced with a manual *Shirodhara* group to prompt out any procedural changes in STAI & POMS. Above articles are strong enough indicative of antianxiety effect of *Shirodhara*, its properties can be used further as preventive, supportive, rehabilitative measure in cancer patients wherein stress plays a major role in its cascade.

DISCUSSION & LIMITATION

This study summarizes the results of multiple studies, it may provide valuable information but can be misleading due to large no. of confounding factors i.e. heterogeneity of results, sample size differences, selection of different studies creating selection bias,

majority of the studies included in were randomized controlled trials, work could have been strengthened by adding observational studies.

The random effect statistical technique was used to analyze the above data with a goal to estimate average effect in the Studies. Well defined objective of knowing antianxiety effect of *Shirodhara* was postulated clearly, Although evaluation of bias and heterogeneity were taken into account, there was a varied possibilities of enhancing the studies by increasing sample size, and creating separate *Shirodhara* group to rule it's obvious effect.

Focus of the studies if restricted to ancient technique could have yielded better and clear defined results, wash out period of *Shirodhara* therapy was not taken into account in most of the studies while assessment of patients in follow-ups, which was a major confounding factor. As the selection of the studies was done by one reviewer. Although there was no restriction in language during the search but only English full text articles were included in this review. There were only seven studies retrieved. All the studies have small sample size, and there was no blinding mentioned in the RCTs it could have altered results. Three of the seven studies were conducted among healthy population, though it showed significant results but there was no involvement of diseased individuals which could have given a much clear insight. All the studies were of short duration and the effect of *Shirodhara* was not counted for long period of time, for more reliable evidences the study should be large enough.

CONCLUSION

It was derived from above data that *Shirodhara* therapy restores the equilibrium of *Sharira* and *Manasika Doshas*.^[20] Which in turn facilitates *Prasannaatmaindreyamanaso* or tranquility of mind, a positive sign of healthy state of the body.

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