Chapter-1

INTRODUCTION

Cancer is a generic name for a large group of diseases with similar pathophysiology, where abnormal cells, typically originating from a single anomalous cell grows beyond their usual boundaries and is capable of invading adjoining parts of the body and re-establish in other organs.

Cancer has become one of the leading non-communicable diseases and cause of deaths worldwide, accounting for 7.6 million deaths (around 13% of all deaths) as reported in 2008. (Brayet al. 2012) Cancer has been on the increase over the past decade, although research continues to understand and prevent it. Better treatment options have enabled patients to manage cancer more efficiently and there is a larger literature available for the importance of quality of life and other psychosocial variables.

Chemotherapy is one among the Conventional cancer treatments, which involves the use of anti-neoplastic cytotoxic agents that target fast growing cells of the body and destroy them. Along with destroying cancerous tissues, several other fast-growing cells like gut micro-flora, stomach mucosal lining, hair follicles, skin epidermal cells etc. are also destroyed. This causes several physical & psychological side effects (Haeset al.1990) that effect majority of patients during chemotherapy. Also chemotherapy can further add up to the psychological distress and majority of these patients show adjustment disorders with symptoms of mixed anxiety and depression. (Gogne et al. 2011).While some side effects like nausea and hair loss are acute and present only during the course of chemotherapy, others like fatigue, anaemia and psychological distress may persist long after and some others like cognitive impairment may present

only much later.(Janelsins et al. 2011) Though Chemotherapy is effectively able to reduce the tumour burden and enables the cancer patients to live longer, it results in several adverse side effects that impair health and quality of life (Hawkins and Grunberg, 2009).The adverse effects are either seen alone or present as a set of associated symptoms, for example nausea and vomiting is frequently associated with loss of appetite and taste alteration. (Barsevick et al. 2006).The intensity of these symptom clusters varies with histopathology, grade and stage of the tumour, the treatment regimen and the type of chemotherapeutic agent used. (Rebecca et al. 2012)

Gastro-intestinal disturbances are invariably seen during chemotherapy and in two previous studies, it has been reported by the patients that nausea is the most concerning adverse event of chemotherapy. Vomiting has been recorded as the third and the fifth most distressing symptom in each of the above studies respectively (Ballatori and Roila 2003). Nausea, very rarely occurs as a single symptom, but emerges along with other symptoms like feeling sick, retching, loss of appetite and abdominal discomfort (GI disturbances) (Dodd et al. 2001, 2004). Anti-emetic medications are fairly effective in controlling vomiting, but nausea still remains the most distressing concern (Ballatori and Roila 2003) and is seen to persist in 70% of the patients undergoing moderately emetogenic chemotherapy (Morrow 1982), (Roscoe et al. 2000) Nausea being a subjective symptom, is less understood and therefore less treated. Many times, temporary inhibition of emesis by the use of anti-emetic drugs often cause an increase in nausea apart from causing other side effects (Osoba et al. 1997), (Feyer & Jordan 2011) & (Roilaet al. 2005)but the use of anti-emetics are necessary in Cancer Chemotherapy induced nausea and vomiting (CCINV). Another significant problem is that, a substantial gap exists between the guidelines for antiemetic therapies and the actual practice (Angeliset al. 2003).

1.1 PATHOPHYSIOLOGY OF CCINV AS PER MODERN CONCEPT

The chemotherapy trigger zone (CTZ) is located in a medullary centre located in the area postrema, which is susceptible to emetic stimuli delivered through the blood or cerebrospinal fluid (CSF)(Andrews 1988)(Miller et al.1994). The chemotherapy trigger zone stimulates the vomiting center, an area of the medulla oblongata that acts by stimulating the phrenic, spinal, and visceral nerves. These efferent signals induce vomiting by their effects on the diaphragm, abdominal muscles, and stomach. The vomiting centre also receives signals of increased intracranial pressure from visceral organs, the inner ear labyrinthine apparatus, and higher CNS structures. The antiemetic's act on chemotherapy trigger zone (CTZ) or on the receptors on gastric mucosal lining and induce gastro- paresis.

Though numerous studies highlight the role of psychological distress and susceptible risk factors in modulating nausea and emesis in cancer patients, they have not been able to address this issue holistically using nausea as a predictable side effect of chemotherapy (Schwartz et al. 1996).

1.2 PATHOPHYSIOLOGY OF CCINV AS PER ĀYURVEDA AND YOGA

Many survivors take to healthy lifestyle changes, like yoga and other alternative therapies, in order to prevent recurrence, improve the quality of life and increase the disease free survival period. Thus, there is an urgent need to understand cancer as described in yoga and other ancient literature and to standardize yoga techniques that are beneficial and feasible for cancer patients. In order to address the problem in a holistic way, we used the concept of "Agni" from Āyurveda scriptures to address this cluster of symptoms as a manifestation of "Agni impairment". Āyurveda is an ancient Indian medical Science that lays emphasis on holistic approach to treatment of diseases

by restoring the homeostatic mechanisms that confer health. Health according to Āyurveda is defined as (a) equilibrium of doṣa′s or vital biological factors that are responsible for metabolic processes in the body, (b) equilibrium in the thirteen components of Agnis that constitute the bio-energy responsible for functional activities of all tissue systems, (c) health of the seven tissue systems or dhātus, (d) proper excretion of waste products of metabolism and (e) restraint over sensory organs with a happy mind and inner peace (Trikamji, 1935Chap 1 Verse 53 & 1981 Chap 15 Verse 44).

According to Āyurveda , diseases are precipitated due to blockage of channels (śrotas) by the stagnation of endotoxins (āma and mala's) that develop due to improper digestion that lead to vitiation of doṣa′s (Haridāsa saṁskrutha granthamāla 106 Chap 13 Verse 25 & 27) Hence, it is necessary that these channels are kept clean and competent. The improper digestion which is the starting point is due to impairment of the gastric fire, the Jāṭharāgni. Āyurveda proposes that all diseases are the result of weak Agni (Amrutheshet al. 2007) and hence the principle of treatment of all diseases is to restore and strengthen all components of Agni that promotes digestion and metabolism. (Divya et al. 2013) So a comprehensive checklist to evaluate impaired Jāṭharāgnilevel in patients with CCINV was developed. Āyurveda texts prescribe correction of doṣa imbalance and Agni ultimately through directing the energy channels - vāyu niyantraṇa (Trikamji, 1935 Chap 28 Verse 3 & 4). So, improving Agni and gastric motility play a vital role in management CCINV. Since the conventional modalities of management adopted for CCINV has not contributed much

to our understanding the complex mechanisms involved in the pathophysiology of CCINV, the present study was planned.

1.3. YOGA FOR CCINV

Yoga intervention has been found to be beneficial in reducing chemotherapy induced nausea and emesis (Raghavendra et al. 2007). A review on cancer patients and survivors has shown physical and psychosocial benefits of Yoga therapy (Buffart et al. 2012).Studies reviewed show that complementary and alternative medicine and mind/body approaches are useful in reducing nausea and emesis either alone or in combination with antiemetic and anxiolytic medications (Mundy et al. 2003 &Reddy et al. 2001).

1.4NEED AND UNIQUENESS OF THIS STUDY

Earlier study done on CCINV andyoga, has shown yoga to help in reducing post chemotherapy nausea and emesis in early breast cancer patients(Raghavendra et al. 2007). The present study is intended to assess the mechanism of action of yoga intervention in managing chemotherapy induced nausea and emesis in patients with different types of cancer receiving different emetogenic chemotherapy regimens. Also the present thesis is an attempt to explore the effect and benefits of yoga therapy on different variables with special reference to its effect on Jāṭharāgni (Agni) in Āyurveda.

Chapter-2

LITERARY RESEARCH

According to Āyurveda and yoga, impairment of jatharāgni and disturbed balance of tridoṣas is considered to be the cause of CCINV. Hence this literature review is focused on compiling the relevant concepts of Āyurveda that led to development of an Āyurveda/yoga based model of CCINV. This chapter offers (i) a review of the literature available in traditional texts of yoga and Āyurveda, on Agni and (ii) an Āyurveda model of CCINV.

Ślokas describing jaṭharāgni and related concepts from Āyurveda and yoga relevant to this study have been compiled from the classical texts in Devanagari script and transliterated to Roman script. Translation and explanation with the relevance of the Ślokas are discussed. The following were the classical texts used for the study:

1. Caraka saṁhitaby Agniveśa,
2. Suśrutasaṁhita,
3. Aṣṭāṅga hridaya and Saṅgraha
4. Śrīmad bhagavadgītā,
5. Patanjali yoga sūtra,
6. Haṭhayogapradīpika,
7. Gheraṇḍa saṁhita,
8. laghu yoga vāsiṣṭha,
9. Atharvaveda.

Based on these concepts, a model of CCINV has been presented.

2.1A REVIEW OF THE LITERATURE AVAILABLE IN TRADITIONAL TEXTS OF YOGA AND ĀYURVEDA ON AGNI

2.1.1 Atharvaveda–Pittaand Agni

आयुर्दा अग्ने जरसं वृणानो घृतप्रतिको घृतघृष्ठो अग्ने ।

घृतं पीत्या मधु चारु गव्यं पितेव पुत्रानभिरक्षतादिमम् ॥

Āyurdā agne jarasaṁ vṛṇāno ghṛtapratiko ghṛtaghṛṣṭho agne।

ghṛtaṁ pītyā madhu cāru gavyaṁ piteva putrānabhirakṣatādimam।।

(Atharvaveda -2/1 3-1)

Lord Agnigives nourishment, knowledge and lusture to the body which correlates with the concept that pitta gives nourishment to the organs.

2.1.2 Caraka saṁhita

अन्नस्य पक्त सर्वेषां पक्रुणमधियो मतःअन्नस्य पक्त सर्वेषां पक्रुणमधियो मतः

तन्मोलस्ते हि तद्वृद्दिक्षयामकाः

annasya pakta sarveṣāṁ paktruṇamadhiyo mataḥ

tanmoolaste hi tadvruddikṣayāmakāḥ

(Caraka saṁhitaChi Ch 15 V 39)

The Agni which digests food is regarded as the master of all Agni ‘s in the body because increase and decrease of other Agni’s depend on this basic Agni.

यदन्न देहधात्वोजोबलवर्णादिपोषकम्

तत्राग्निर्हेतुराहारान्न त्यपक्वाद्रसादयः

yadanna dehadhātvojobalavarṇādipoṣakam

tatrāgnirheturāhārānna tyapakvādrasādayaḥ

(Caraka saṁhitaChi Ch 15 V 5)

The food nourishes dhātu's, ojas, strength, complextion etc. Dhātu's cannot be produced from undigested food.

अन्नमादानकर्मा तु प्राणः कोष्टं प्रकर्षति। तद्द्रवैर्भिन्नसंघातं स्नेहन म्रुदुतां गतम्।

समानेनावधूतोग्निरुदर्यः पवनेन तु। काले भुक्तं समं सम्यक् पचत्यायुर्विव्रुद्दये।

एवंरसमलायन्नमाशयस्थमधःस्थितः।पचत्यग्निर्यथाथाल्यामोदनायाम्बुतण्डुलम्।

annamādānakarmā tu prāṇaḥ koṣṭaṁ prakarṣati। taddravairbhinnsaṁghātaṁ snehana mrudutāṁ gatam।

samānenāvadhūtoagnirudaryaḥ pavanena tu। kāle bhuktaṁ samaṁamyakpacatyāyurvivruddaye। evaṁsamalāyannamāśayasthamadhaḥsthitaḥ। pacatyagniryathā sthālyāmodanāyāmbutaṇḍulam।

(Caraka saṁhitaChi Ch 15 V 6-8)

The component of prāṇavāyuthat has receiving functions, carries the food to the belly where the food is disintegrated by fluids (juices) and softened by fatty substances, gets acted upon by the digestive fire, fanned by the samāna vāyu.Then the digestive fire cooks the balanced food that is consumed properly leading to promotion of life span. Agnicooks the food from below;is situated in the stomach and divides it intorasa(nutritive fraction) andmala(excretion) similar to the fire that cooks the rice grains at the bottom of water in a vessel to come up as boiled rice.

व्यायामतीक्ष्णौषधशोकरोगभयोपवासाघातिकर्शितस्य।

वयुर्महास्त्रोतसि संप्रव्रुद्ध उत्क्लेश्य दोषांस्तत उर्द्वमस्यन्।

vyāyāmatīkṣṇauṣadhaśokarogabhayopavāsāghātikarśitasya।

vayurmahāstrotasi sampravruddha utkleśya doṣāṁstata urdvamasyan।

(Caraka saṁhita Chi Ch 20 V 7)

In a person emaciated due to physical exercise, irritant drugs, grief, illness, fear, fasting etc, the vitiated (aggravated) vāyu in mahāsrotas (gastrointestinal Tract) throws up the doṣa‘s (impure contents) upwards to excrete the mala which causes vomiting. the gastric irritation also produces the discomfort that appears as pressure in the cardiac region.

अग्निरेव शरिरे पित्तान्थर्गतः

agnireva śarire pittānthargataḥ

Caraka views that Agniin the body is implicit in Pitta

(Caraka saṁhita Chi su 12 V 11)

अग्निम् जरण शत्त्या परीक्षेत

agnim jaraṇa śaktyā parīkṣeta

(Caraka saṁhitaVi Ch 4 V 8)

According to Caraka the efficient function of Agni has to be determined by the capacity of an individual to digest and utilize the food ingested.

2.1.3 Aṣṭāṅga hridayaand AṣṭāṅgaSaṅgraha

त्यक्त द्रवत्वम् पाकादि कर्मण अनल शब्दितम्

tyakta dravatvam pākādi karmaṇa anala śabditam

(Aṣṭāṅga hridaya. Su 12 V 10)

Pācaka pitta although present as a liquid but still it performs action similarto Agni like digestion of food.

लाघवम् कर्मसामर्थ्यं दीप्तोग्नि मेदसः क्ष्यः।

विभिक्तघनगात्रत्वम् व्यायामादुपजायते।

lāghavam karmasāmarthyaṁ dīptoagni medasaḥ kṣyaḥ।

vibhiktaghanagātratvam vyāyāmādupajāyate।

(Aṣṭāṅga Saṅgraha Su Ch 2 V 10)

That which brings lightness, enhances capacity to work, that which increases Agni, that which reduces fat and which makes the body solid and strong is known as vyāyāmā

2.1.4 Agni according to Bhagavadgītā

अहं वैश्वानरो भूत्वा प्राणिनां देहमाश्रितः

प्राणापानसमायुक्तः पचाम्यन्नं चतुर्विधम्

ahaṁ vaiśvānaro bhūtvā prāṇināṁ dehamāśritaḥ

prāṇāpānasamāyuktaḥ pacāmyannaṁ caturvidham

(Gītāh 15 V 14)

I, having become (the fire) vaiśvānara, abide in the body of beings, and associated with prāṇa and apāna, digest the four-fold food

.

2.1.5 Haṭha yogapradīpika

हठस्य प्रथमांगत्वदासनं पूर्वमुच्यते।

कुर्यात्तदासनं स्थैर्यमारोग्यं चांगलाघवम्॥

haṭhasya prathamāṅgatvadāsanaṁ pūrvamucyate।

kuryāttadāsanaṁ sthairyamārogyaṁ cāṅgalāghavam।।

(Haṭha yogaCh āsana V 17)

Prior to everything, āsana is spoken of as the first part of Haṭha yoga. Having done āsana one gets steadiness(firmness) of body and mind; diseaselessness and lightness (flexibility) of the limbs.

The explanation is similar to the reference of importance and benefits of vyāyāmā of Aṣṭāṅga hridayasūtrasthāna wherein increase of Agni is mentioned as one of the

benefits. In Haṭha yogaāsana is a specific position which opens the energy channels and psychic centres. Haṭha yogais a process through which purification and control of the body take place by restructing the prāṇa flows.

यथेष्टंन्धारणं वायोरनलस्य प्रदीपनम्

नादाभिव्येक्तिरारोग्यं जायते नाडिशिोधनात्

yatheṣṭannghāraṇaṁ vāyoranalasya pradīpanam

nādābhivyektirārogyaṁ jāyate nāḍiśodhanāt

(Haṭha yogaCh 2 V 20)

One is able to hold thevāyuaccording to one's will, the analapower increases. With the nāḍi 's purified, thus the inner nādā awakens and one is free from diseases.

2.1.6 Geraṇda saṁhita

बहु कदशनभुक्तं भस्म कुर्याद्शेषं जनयतिजठराग्निं जारयेत्कालकूटम्।

हरति सकल रोगानाशु गुल्मज्वरादीन्नभवति विगतदोषमासनं श्रीमयूरम्

bahu kadaśanabhuktaṁ bhasma kuryādśeṣaṁ janayatijaṭharāgniṁ

jārayetkālakūṭam।

harati sakala rogānāśu gulmajvarādīnnabhavati vigatadoṣamāsanaṁ śrīmayūram

(Geraṇda saṁhitaCh 2 V 30)

The peacock –posture destroys the effects of unwholesome food ; it produces heat in the stomach; it destroys the effects of deadly poisions; it easily cures diseases, like gulma and fever; such is this useful posture.

2.1.7 Laghu yoga vasiṣṭa

सन्क्षोबात्साम्यमुत्सृज्य वहन्ति प्राणवायवह।

असमे वहति प्राणे नड्यो यान्ति विसम्स्थितिम्॥

sankṣobātsāmyamutsrujya vahanti prāṇavāyavaha।

asame vahati prāṇe naḍyo yānti visamsthitim।19।

दोशा ऐव प्रयात्यन्नं नाडिप्राणविपर्यात्।

यान्यन्नानि विरोधेन तिस्टन्तः शरीरके।

doṣā yaiva prayātyannaṁ nāḍiprāṇaviparyāt।
yānyannāni virodhena tiṣṭantaḥ śarīrake।20 ।

(Laghu yoga vasiṣṭa V 19 20)

When the ‘manas’ is agitated then this body also follows in its wake. And when the body is agitated then there is no proper perception of the things that are in one’s way and prāṇaflies from its even path on to a bad road, staggering like an animal wounded by an arrow. Through agitation, prāṇa, insted of pervading the whole body steadily and equally, vibrates every where at an unequal rate. Therefore the nāḍi′sdo not maintain a steady position, but quirer . This disturbances of prāṇa in nāḍi′sresults in irregular incomplete or excessive digestion. The badly digested food which settles down in this body amidst such commotion, is transffered into incurable diseases. Thus through the primary cause (of the mind) the disease of the body is generated. If this primary cause is annihilated at its rootthen all diseases will be destroyed.While describing the cause of disease importance of Agni is enumerated.

2.1.8 Patanjali yoga sūtra

योगः चित्तव्रुत्तिनिरोधः

yogaḥ cittavruttinirodhaḥ

Process of gaining control over mind

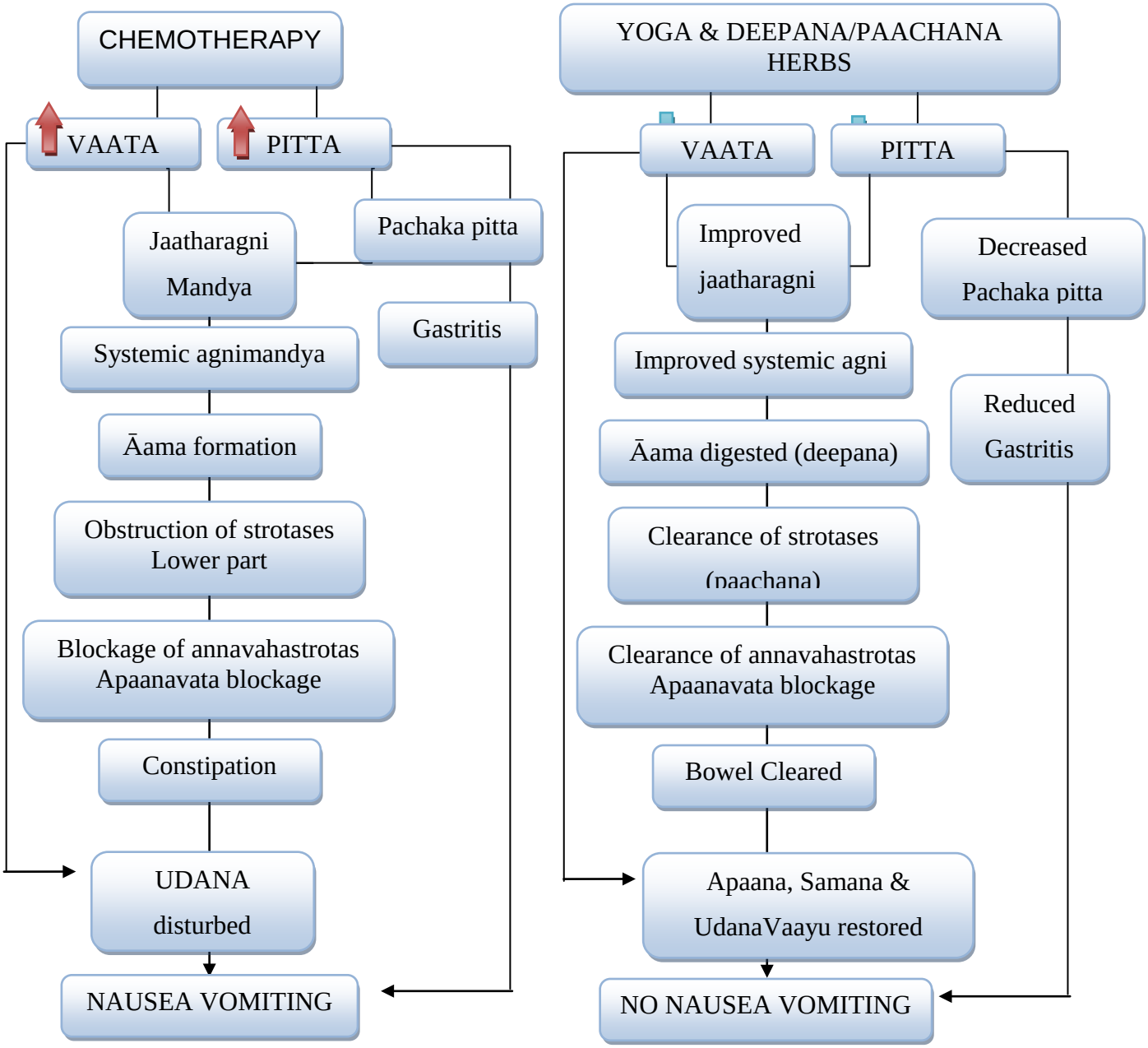
(Patanjali yoga sūtra Ch1 V2)

2.2 THE MODEL OF CCINV

Chemotherapy causes several distressing symptoms ranging from nausea and vomiting to low blood counts which are understood as disturbances in five components of health, namely doṣā, Agni, dhātu, malakriya, and manas-ātma-indriya. The pathophysiology of CCINV can be holistically explained by Āyurveda by the following model.

Āyurveda proposes that chemotherapy induces aggravation of both vāta and pittadoṣā 's (Metri et al. 2014) Aggravated pitta results in heightened activity of pācaka pitta situated in the stomach region which is responsible for gastritis and jāṭharāgnimāndya (poor gastric fire manifesting as poor appetite).The associated aggravation of vātadoṣā contributes to worsening of the jāṭharāgnimāndya and also leads directly to aggravation of udānavāta which is located in the chest and causes vomiting.

FIG 2.1 :ĀYURVEDA/YOGA MODEL OF CCINV



Yoga is defined as voluntary mastery over all functions of the mind (yogaḥ cittavruttinirodhaḥ, Patanjali) through conscious voluntary slowing down of the rate of flow thoughts (manaḥpraśamanaupāyaḥ, vasiṣṭa) to achieve balanced functioning of the mind (samatvam yoga ucyate, Bhagavadgītā). Thus yoga brings balance at all levels by slowing down and rest at all levels. There are several herbs [e.g.pippali, śuṇṭhi etc.] recommended for reducing Jāṭharāgni māndhya. As the excited pitta gets cooled down, the pācaka pitta activity reduces which helps in reducing gastritis. Reduction of excited pācaka pitta activity also improves jaṭarāgni .This in turn improves the functioning of other Agni [dīipana]. This helps in digestion of accumulated āma at all levels. This further clears the srotas, relieves constipation by normalizing the flow of apāna and udāna vāyu. A good clearance of the bowel reverses the vāyu flow and stops the nausea and vomiting. Thus the Āyurveda concept proposes a reversibility model of CCINV and emphasizes on correcting the Agnimāndhya while yoga offers correction of vāta imbalances through breathing techniques that corrects the master vāta, the prāṇavāta.

Chapter-3

LITERATURE SURVEY

This chapter has compiled relevant literature available on CCINV and all literature till date on the work done on yoga and mind body interventions in cancer.

Effects of CCINV on treatment compliance:

There is a high prevalence rate in nausea and emesis following chemotherapy. This is attributed to high doses of emetogenic antineoplastic agents and anticipatory nausea and emesis (King et al. 97).Distressing symptoms such as nausea, vomiting, retching, anorexia, motion sickness, headaches etc. commonly occur following chemotherapy and antiemetogenic administration. These distressing symptoms can impede the ability of the patients to perform normal household tasks, enjoy meals and maintain daily function and recreation thereby reducing their quality of life.(Osoba, et al. 1997). Some patients may even see the treatment and resulting distress worse than the disease itself (Rimer, Jones & Blumberg et al. 1983) while some may even discontinue the prescribed course of chemotherapy(Burish and Tope, 1992), thereby reducing hope of recovery and life expectancy(Gilbar, 1991).

3.1 DEFINITION:

Nausea and vomiting can be divided into three categories: Nausea, Retching, and Vomiting. Whereas retching and vomiting are brainstem responses, nausea involves higher brain regions and is not well understood.

Nausea is subjective and consists of an urge to vomit. It may be accompanied by autonomic symptoms such as pallor, tachycardia, diaphoresis, and salivation. Nausea is a protective reflex against the ingestion of toxins and is defined as a subjective

phenomenon of an unpleasant sensation in the epigastrium and in the back of the throat that may or may not culminate in vomiting (Rhodes and McDaniel,1997).

Retching is the rhythmic contractions of the diaphragm, abdominal wall, and chest muscles that precede vomiting, although the latter is a reflexive, rapid, and powerful ejection of upper gastrointestinal tract contents resulting from vigorous and continuous contractions of the abdominal and thoracic muscles (Hawkins and Grunberg, 2009). Vomiting is the "mechanical result of neurophysiologically induced rhythmic, coordinated, diaphragmatic, chest wall and abdominal muscle action leading to expulsion of gastric contents through the mouth" (Fessele,1996).

3.2 CLASSIFICATION:

CCINV is a complex phenomenon, and there are 5 generally recognized types that require different management strategies:

3.2.1 Acute CCINV: occurs less than 24 hours after chemotherapy.

3.2.2 Delayed CCINV: vomiting occurring >24 hours or more after chemotherapy which can persist for several days. The designation of acute and delayed CCINV as distinct is more than mere timing; physiologic differences exist in the pathways involved in these two forms of CCINV.

Note: Acute CCINV appears to be mediated primarily by serotonin pathways, delayed CCINV is more substance P mediated.

3.2.3 Anticipatory CCINV: As the name implies, anticipatory emesis develops before chemotherapy is given It is a learned response that arises secondary to a history of poorly controlled CCINV. It may be triggered by tastes, odors, sights, thoughts, or anxiety associated with chemotherapy. Anticipatory CCINV is more difficult to control

than acute or delayed CCINV, and its treatment may include the use of behavioral therapy or benzodiazepines.

3.2.4 Breakthrough CCINV: Breakthrough CCINV, as the name implies, is nausea and vomiting that occurs despite antiemetic therapy and requires rescue medication.

3.2.5 Refractory CCINV: is the term used when patients have failed antiemetic prophylaxis and/or rescue medications in previous chemotherapy cycles and have emesis in succeeding cycles.

3.3 IMPACT OF CCINV:

CCINV can result in weakness various side effects and is associated with a variety of complications, including, physical and mental deterioration, and wound dehiscence (Navari, 2007) and (Hamadani et al. 2007). It negatively affects patients' nutritional habits, abilities to work, and motivation to follow recommended treatment regimens (Roscoe et al.2010**)**. Uncontrolled CCINV can give rise to medical complications, including poor nutrition, dehydration, electrolyte imbalances, and physical and mental deterioration. (Hamadani et al. 2007)

Amongst different types of CCINV, antiemetic treatments have been less effective in improving delayed nausea and vomiting than acute nausea and vomiting (Bloechl-Daum, et al. 2006). Delayed nausea commonly occurs following the administration of cisplatin, carboplatin, cyclophosphamide, or doxorubicin. (Gralla et al. 1999). Incidence rates for anticipatory nausea and vomiting range from 18% to 57%, with nausea occurring more frequently (Navari, 2007).

When CCINV is poorly or uncontrolled, the possible emergency department visit or visits to healthcare practitioner's office that may arise during the course of treatment

can have profound economic impact (Tina Shih and Elting. 2007) on the patients. Some patients may even see the treatment and resulting distress worse than the disease itself (Rimer, Jones & Blumberget al. 1983), while some may even discontinue the prescribed course of chemotherapy (Burish and Tope, 1992)., thereby reducing hope of recovery and life expectancy (Gilbar,1991).

3.4 EFFECTS OF CCINV ON TREATMENT COMPLIANCE:

There is a high prevalence rate in nausea and emesis following chemotherapy. This is attributed to high doses of emetogenic antineoplastic agents and anticipatory nausea and emesis (King, et al. 1997).Yoga helps to reduce post chemotherapy nausea and emesis in early breast cancer patients (Raghavendraet al. 2006).

3.5 RISK FACTORS:

Numerous risk factors for chemotherapy-induced nausea and vomiting (CCINV) have been identified (Roscoe et al. 2010). Chemotherapy and patient-specific risk factors can help identify the risk of emesis. It depends on:

3.5.1 Drugs given: Cytotoxic anti neoplastic agents vary greatly in their potential to induce emesis and in the severity of this side effect. In general, the drugs that are most likely to cause emesis also tend to cause the most severe emesis. Generally, agents that cause emesis in more than 30% to 40% of patients are considered to have high emetogenic potential, whereas those with less than a 10% incidence are considered to have a low potential.

3.5.2 Patient factors: Individual patients also vary considerably in the degree of emesis they experience after chemotherapy. It is important to take a detailed history before

starting a patient on chemotherapy, since certain clinical factors may increase or decrease the risk of developing treatment-induced emesis. These factors include:

3.5.2.1 ***Age and Gender:*** The strongest risk factor is generally assumed to be younger age and female gender, since younger patients are more likely to develop dystonic reactions to dopamine-blocking agents, which are often used to prevent and treat chemotherapy-induced emesis. Women experience more chemotherapy-associated emesis than men. Although the reason for this is uncertain, it may be because women are more likely than men to receive combination chemotherapy because these regimens are more commonly used for malignant diseases that mostly afflict women, such as breast cancer.

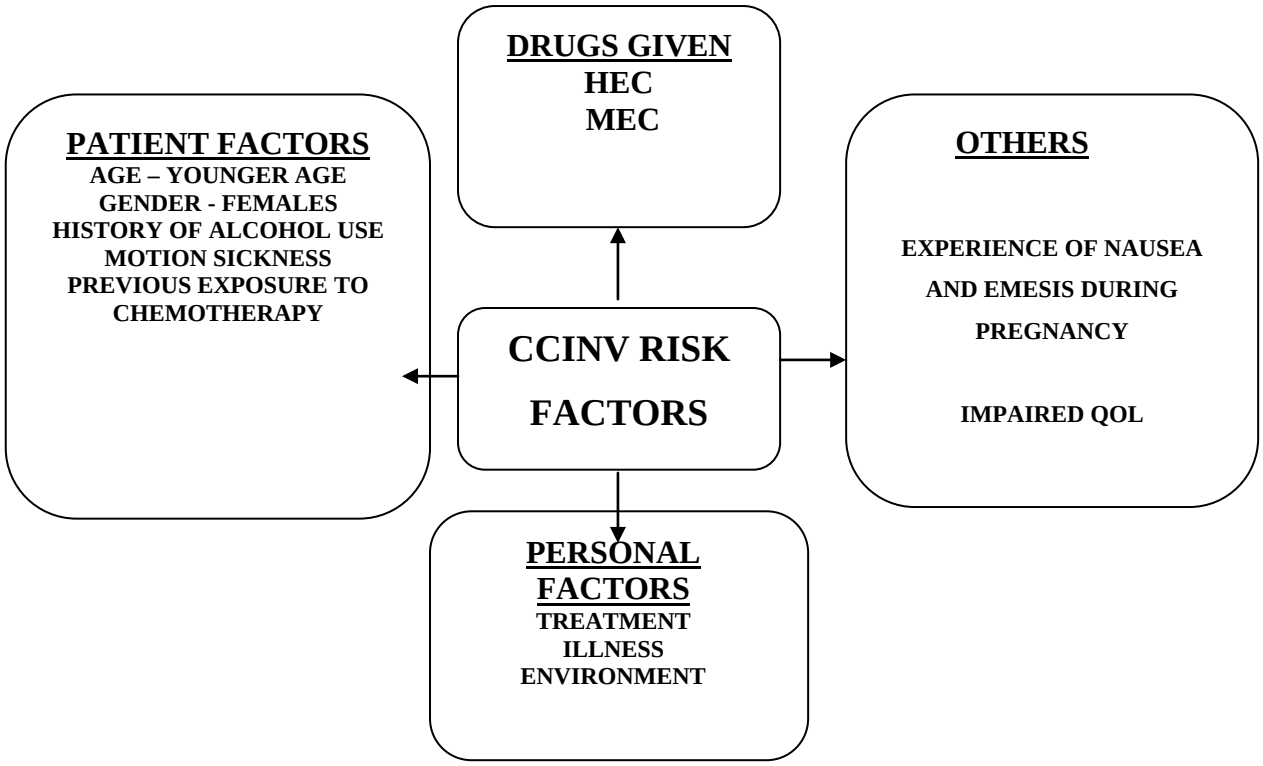
3.5.2.2 ***History of alcohol use:*** Patients with a history of chronic alcohol intake also have influence on CCINV.

3.5.2.3 ***Motion sickness:*** Patients with a history of motion sickness have a greater risk. Concomitant radiation therapy and previous exposure to chemotherapy increase the risk. Non–chemotherapy-related causes of emesis must be considered in patients who experience nausea and vomiting while receiving an antineoplastic drug. These include bowel obstruction, renal insufficiency, brain metastases, or other medications (eg, narcotic analgesics) (Markman. 2002).

3.5.3 Personal factors: Factors related to treatment, illness, and environment greatly influence nausea and vomiting. The symptoms occurred less in a quiet and relaxing ward and younger patients without domestic disputes experienced the symptoms less often (Phianmongkhol and Suwan, 2008).

3.5.4 Others: Other than the above, experience of nausea and emesis during pregnancy, impaired QOL, greater anxiety and previous experience with chemotherapy have all shown significant correlations with subsequent CCINV (Roscoeet al. 2010).

Fig3.1: SUMMARY OF RISK FACTORS



3.6 NAUSEA AND VOMITING AS ADVERSE EVENTS AND GRADING

An Adverse Event (AE) is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses(CTCAE.2009). In two studies, nausea ranks number **1** as the adverse event of chemotherapy of most concern to patients, with vomiting ranking as the **3rd and the 5th** most distressing symptom (Ballatori&Roila, 2003).

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Table 3.1: Grading for adverse events

Grade 1	Mild asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Abbreviation: Activities of Daily Living (ADL)

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Table 3.2: Grading for Nausea and Vomiting

ADVERSE EVENT	GRADING				
	1	**2**	**3**	**4**	**5**
NAUSEA	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	Not available	Not available
EMESIS	1 – 2 episodes (separated by 5minutes) in 24 hrs	3 - 5 episodes (separated by 5minutes) in 24 hrs	>=6 episodes (separated by 5minutes) in 24 hrs; tube `feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

3.7 PSYCHOLOGICAL ISSUES (EFFECT OF NAUSEA & EMESIS ON MIND AND VICE VERSA)

Stress has been defined as the inability to cope with a perceived threat to one's mental, physical, emotional, and spiritual well-being (Hartfiel, et al. 2011). The diagnosis of cancer and its treatment have been shown to have profound effects on the psychological status of patients (Gogneet al. 2011) exhibiting stress, anxiety, depression and loss of control Phianmongkhol and Suwan, 2008).

Various studies have shown risk factors such as motion sickness, vomiting related to particular foods, pretreatment anxiety and expectations (Jacobsonet al. 1988) and (Morrow et al. 1991) to have a strong predisposition for post chemotherapy and

anticipatory nausea and vomiting and these can further exacerbate the responses to conditioned stimuli in these subjects (Matte et al. 1987) Therefore, these strong relationships between psychosocial variables, autonomic dysfunction and nausea and emesis justify the need for integrating mind body therapies with pharmacological interventions in managing treatment related nausea and emesis (Schwartzet al. 1996)

3.8 CCINV AND QOL

CCINV affects different patients in varying degrees. The effects on QOL are greatest when CCINV is severe and long lasting, interferes with activities of daily living, (Bloechl-Daum , et al. 2006) magnifies the other toxicities of treatment resulting in poor compliance with the treatment regimen, (Markman, 2002) and (Navari,2007) Similarly, delayed nausea and vomiting adversely impact patient's quality of life. (Bloechl-Daum ,et al. 2006) Patients treated with highly emetogenic chemotherapy (HEC) reported significantly lower mean HRQL compared to patients treated with moderately emetogenic chemotherapy (MEC) (Hilarius et al. 2011).

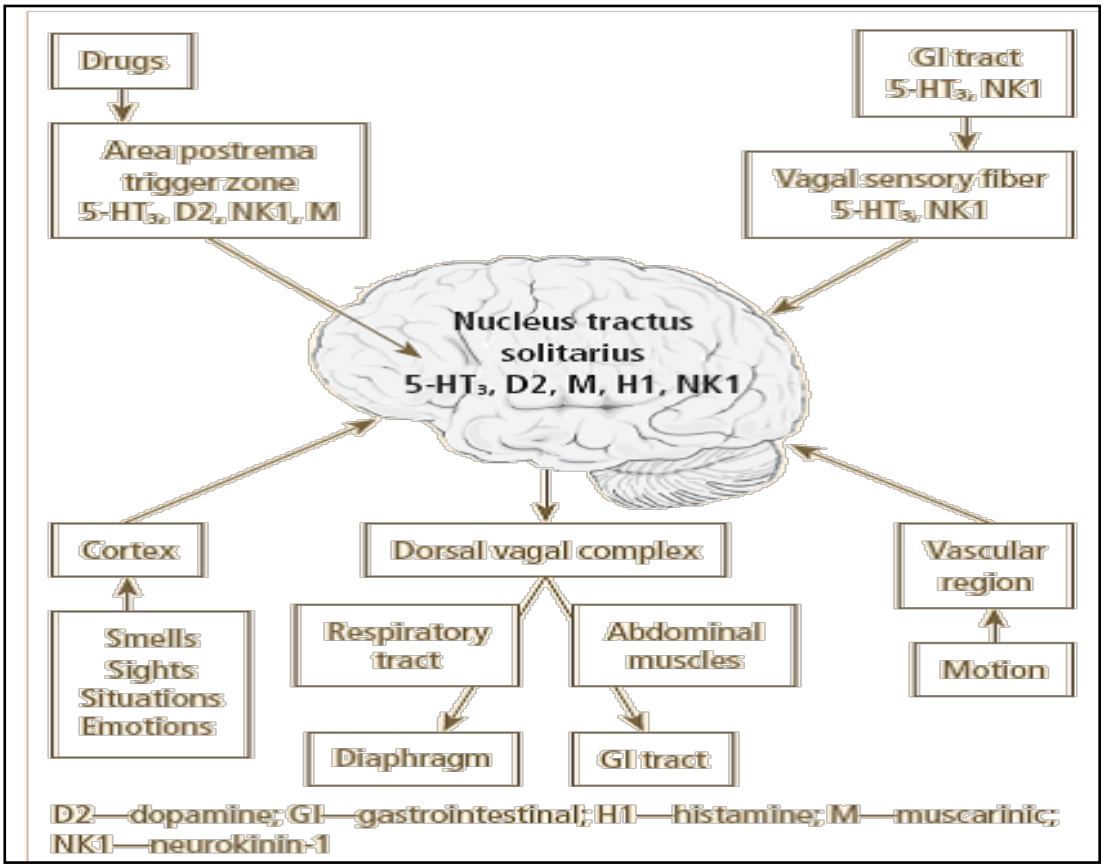
Adopting preventive measures for CCINV like supportive care-clinical treatments, behavioral interventions (Demark-Wahnefried 2007) or interventions such as counseling, providing social support (Montazeri, 2008) starting from the first day of chemotherapy itself may contribute to maintain a good quality of life and adequate caloric intake, which in turn reflects as an increased ability to complete household tasks, maintain daily functioning, complete chemotherapeutic treatment (Bajettaet al. 2009) and promote social activity (Hatake , 2011)

It is now well documented that yoga and meditation help in stress reduction. Furthermore, yoga has been shown to improve not only the quality of life of healthy subjects but also patients suffering from variety of ailments, including pulmonary

disorders , cardiovascular dysfunctions, cancer, diabetes, rheumatoid arthritis, menopause, and schizophrenia (Rakhshaniet al. 2007)

3.9 MECHANISM OF EMESIS AND PATHO-PHYSIOLOGY OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING:

Fig 3.2The Pathophysiology of Chemotherapy induced Nausea and Vomiting:Emetic Pathways and the Vomiting Center



The act of vomiting involves a reflex arc. Signals sent to the dorsal vagal complex activate somatic and visceral impulses to the effector organs: abdominal muscles, stomach, oesophagus, and diaphragm. Once the vomiting center is stimulated, the airways close and respiration is markedly lowered. The upper oesophagus relaxes and an increase in intra-abdominal pressure occurs, leading to the expulsion of the gastric contents.

Activation of the vomiting center may occur as the result of afferent input from drugs, such as chemotherapeutic agents, motion, smells, sights, situations, and emotions, as well as from gastrointestinal input.

The vomiting center has three main components (the area postrema, the nucleus tractussolitarius, and the dorsal vagal complex) that integrate the emetic responses. CCINV may result from the presence of chemotherapeutic agents or their metabolites in the blood stream or the cerebrospinal fluid that acts directly on the chemoreceptor trigger zone in the area postrema. This area lies outside the blood-brain barrier and is, therefore, sensitive to blood-borne and cerebrospinal fluid borne stimuli. Signals from the area postrema are then relayed to the nucleus tractussolitarius, which lies within the blood-brain barrier and relies on neurotransmitters to trigger emesis. Cytotoxic agents also may induce release of serotonin and substance P from the enterochromaffin cells of the gastric mucosa, which then send signals to the nucleus tractussolitarius via vagal sensory fibers. Following stimulation of the nucleus tractussolitarius, the vomiting response is mediated by efferent pathways, including the vagus and phrenic nerves. Current thinking is that, rather than a well-defined anatomic area, the vomiting center exists as interconnecting neural networks that penetrate into the nucleus tractussolitarius. In addition to the serotonin (5-HT3) and substance P (NK1) pathways, cannabinoid and dopamine (D2) pathways also are involved in CCINV. Other pathways involved in nausea and vomiting include acetylcholine or muscarinic (M), histamine (H1), endorphin, and g-aminobutyric acid, but these do not appear to be activated in CCINV. Figure 1 illustrates the metabolic pathways and receptors involved in the pathophysiology of emesis and CCINV (Hawkins and Grunberg.2009)

3.10 MANAGEMENT: ANTI EMETIC, APREPITANT, ANXIOLYTICS, STEROIDS

CCINV management has become a fertile area for pharmacological research, resulting in a range of antiemetic interventions undreamt of 20 years ago, and the development of evidence-based treatment strategies supported by international guidelines. It has been recommended that the CCINV risk for every patient should be assessed before chemotherapy is administered, and appropriate prophylactic measures should be taken, based on the latest guidelines.

The cornerstone of current recommendations for CCINV management is effective prophylaxis, i.e. treatment given before the patient develops the first symptoms of nausea or vomiting. The latest international guidelines 2011 updates to recommendations from the Multinational Association of Supportive Care in Cancer (MASCC) and the National Comprehensive Cancer Network (NCCN) set out a multi-drug approach to CCINV prophylaxis for patients receiving HEC (Highly emetogenic chemotherapy) and MEC (Moderately emetogenic chemotherapy) regimens (Tables 3.3 and 3.4).

Table 3.3: CCINV Prophylaxis guidelines for patients receiving HEC regimens

Guideline	Drug combination on day of chemotherapy	Drug combination on day 2 + after chemotherapy
MASCC	Aprepitant + 5HT3RA + dexamethasone	Dexamethasone + aprepitant
NCCN	NK-1 RA + 5HT3 RA + dexamethasone ± lorezepam ± H2 blocker or proton pump inhibitor	NK-1 RA + dexamethasone ± lorezepam ± H2 blocker or proton pump inhibitor

MASCC, Multinational Association of Supportive Care In Cancer; NCCN, National Comprehensive Cancer Network; 5HT3- RA, 5-hydroxytryptamine type 3 receptor antagonistic; NK-1 RA, neurokinin -1 receptor antagonistic.

Table 3.4: CCINV Prophylaxis guidelines for patients receiving MEC regimens

Guideline	Drug combination on day of chemotherapy	Drug combination on day 2 + after chemotherapy
MASCC	**Palonosteron + dexamethasone**	**Dexamethasone**
NCCN	**5HT3 RA + dexamethasone ± NK-1 RA in selected patients ± H2 blocker or proton pump inhibitor**	**5HT3 RA (unless NK – RA used on day 1) or dexamethasone or NK-1 RA in selected patients ± lorezepam ± H2 blocker or proton pump inhibitor**
MASCC, Multinational Association of Supportive Care In Cancer; NCCN, National Comprehensive Cancer Network; 5HT3- RA, 5-hydroxytryptamine type 3 receptor antagonistic; NK-1 RA, neurokinin -1 receptor antagonistic.		

The key drug classes are 5-hydroxytryptamine type 3 receptor antagonists (5HT3 RAs), neurokinin-1 receptor antagonists (NK-1 RAs) and corticosteroids. Within these classes, MASCC specifically recommends the NK-1 RA aprepitant for both HEC and MEC and, in its MEC guidelines; it specifies the 5HT3 RA palonosetron on day 1 of chemotherapy. Both 2011 guidelines indicate dexamethasone as the corticosteroid of choice (Vidall et al.2012)For interpretation of the use of antiemetic, combinations of antiemetic were categorized in accordance with international guidelines. From these guidelines, six combinations can be defined:

1. A combination of a 5HT3 antagonist, a corticosteroid and aprepitant
2. A combination of a 5HT3 antagonist and a corticosteroid
3. A 5 HT3 antagonist
4. A corticosteroid
5. Aprepitant and a corticosteroid

6. Other antiemetics (for example metoclopramide or a benzodiazepine) (Hilarius&, Kloeg, 2011).

3.11 MECHANISM OF ACTION OF MEDICATION IN MANAGEMENT OF CCINV

A review article focuses on the current understanding of CCINV, problems associated with its management and the status of promising antiemetic therapies. A wide variety of antiemetic agents are available for the prevention and treatment of CCINV. Combination antiemetic regimens have become the standard of care for the control of CCINV.

3.11.1 5-HT3 Receptor antagonists: Antagonists inhibiting the actions of serotonin have been the most widely used antiemetic for the management of CCINV over the past 20 years. Five 5-HT3 receptor antagonists (5-HT3-RAs) are currently available in Europe and the United States: ondansetron, granisetron, tropisetron, dolasetron and, more recently, palonosetron. When given at equivalent doses for the prevention of acute emesis, 5-HT3-RAs have equivalent efficacy and safety and can be used interchangeably. Single-dose daily schedules have similar efficacy to multiple dose daily schedules, and oral forms have been shown to be as effective as IV forms. As a class, 5-HT3-RAs are well tolerated; common adverse events include mild headache, transient elevation of hepatic aminotransferase levels and constipation.

All five currently available 5-HT3-RAs are effective in controlling acute CCINV in patients receiving HEC or MEC regimens. Despite this, 5-HT3-RAs are not universally accepted as standard prophylactic therapy for delayed CCINV. However, this might not be the case with palonosetron. A meta-analysis from 2005 reported that 5-HT3-RAs

(palonosetron was not included in the metaanalysis) did not significantly improve control of delayed CCINV.

In view of this, current guidelines recommend that dexamethasone should be the agent of choice for delayed CCINV associated with MEC [excluding regimens containing anthracycline (AC) / cyclophosphamide], with 5-HT3-RAs used as alternative agents.

3.11.2 Neurokinin1 Receptor Antagonists: The first NK1-RA aprepitant was first approved in 2003. They exert their antiemetic action through the inhibition of substance P in the emetic pathways in both the central and peripheral nervous systems. Aprepitant is currently the only agent available in this class, although a novel NK1 RA, namely casopitant, has shown clinical promise in phase III trials of patients receiving MEC and HEC. Other NK1-RA, such as netupitant and rolapitant, are also under investigation.

Aprepitant is available for oral and as fosaprepitant in the I.V. administration form. Aprepitant is well tolerated. The most common low-grade adverse effects reported during clinical trials include headache, anorexia, fatigue, diarrhoea, hiccups and mild transaminase elevation (Gilbar1991), (King et al. 1997), (Osoba et al. 1997) (De Angelis et al. 2003) and (Roilaet al. 2005). In general, the incidence of adverse events reported with aprepitant plus 5-HT3-RA and dexamethasone is similar to that with 5-HT3-RA plus dexamethasone alone: Potential interaction appears to be rather low.

3.11.3 Corticosteroids: Corticosteroids are an integral part of antiemetic therapy for acute and delayed CCINV, although they are not approved as antiemetics. When used in combination with other antiemetics, corticosteroids exert a booster effect, raising the emetic threshold. Dexamethasone is the most frequently used corticosteroid,.

Steroids are sometimes underutilized, owing to concerns regarding potential adverse events. Usually, when used in the short term as antiemetic therapy, corticosteroids are well tolerated.

Studies have concluded that in patients treated with a single injection of palonosetron on day 1 in combination with dexamethasone on day 1 only might be a sufficient treatment option also in view of the delayed phase.

3.11.4 Dopamine Receptor Antagonists: Prior to the introduction of 5-HT3-RAs, dopamine receptor antagonists formed the basis of antiemetic therapy. These agents can be subdivided into phenothiazines, butyrophenones and substituted benzamides. One of the most frequently used benzamides is metoclopramide. Before establishing the 5-HT3-RAs in CCINV prophylaxis, metoclopramide, usually at high doses and in combination with a corticosteroid, played a primary role in the management of acute CCINV. However, in patients receiving cisplatin-based chemotherapy, the effects of conventional doses of metoclopramide are not significantly different from placebo. Consequently, current guidelines do not recommend metoclopramide for prevention of acute CCINV. Although not effective in the acute phase, metoclopramide in combination with corticosteroids has proven efficacy in the prevention of delayed CCINV. Indeed, two studies have demonstrated that metoclopramide-containing regimens are more effective than corticosteroid monotherapy. In the study by the Italian group for antiemetic research, the combination of metoclopramide plus corticosteroid was shown to be as effective as 5-HT3-RA plus corticosteroid in the delayed phase (CR 60% versus 62%). Consequently, metoclopramide was recommended for the prevention of delayed CCINV by the first MASCC and former ASCO antiemetic guidelines. However, in the updated MASCC/European Society for

Medical Oncology (ESMO) and current ASCO guidelines, metoclopramide is no longer recommended for use in the prevention of delayed CCINV, due to the availability of more effective drugs, such as NK1-RA. The current ASCO guidelines recommend that metoclopramide be reserved for patients intolerant of or refractory to 5-HT3-RAs, dexamethasone and aprepitant.

3.11.5 Benzodiazepines: Benzodiazepines can be useful additions to antiemetic regimens in certain circumstances. They are often used to treat anxiety and reduce the risk of anticipatory CCINV. Benzodiazepines are also used in patients with refractory and breakthrough emesis.

3.11.6 Cannabinoids: Cannabinoids (e.g. dronabinol and nabilone) possess weak antiemetic efficacy combined with potentially beneficial side effects, including sedation and euphoria. This makes them a useful adjunctive therapy in selected patients; in the ASCO and NCCN guidelines, cannabinoids are recommended for patients intolerant of or refractory to 5-HT3-RA or steroids and aprepitant. In a systematic review of the efficacy of oral cannabinoids in the prevention of nausea and vomiting, cannabinoids were found to be slightly better than dopamine receptor antagonists, including phenothiazines, haloperidol and metoclopramide. Despite this, their clinical utility was found to be generally limited by the high incidence of adverse events, such as dizziness, dysphoria and hallucinations (Feyer and Jordan, 2011).

3.12 EMETIC RISK OF CHEMOTHERAPY DRUGS DETERMINED BY FREQUENCY OF EMESIS:

Table 3.5 lists intravenous agents organized by emetic risk (51) (Antiemetics ASCO, 2011)

High risk = >90% frequency of emesis, Moderate = >30-90%, Low = 10-30%, Minimal = <10%.

Table 3.5: Emetic risk of commonly used IV drugs

High	Moderate	Low	Minimal
Carmustine	Azacitidine	Fluorouracil	2-Chloro-deoxyadenosine
Cisplatin	Alemtuzumab	Bortezomib	Bevacizumab
Cyclophosphamide >1,500 mg/m2	Bendamustine	Cabazitaxel	Bleomycin
	Carboplatin	Cytarabine<1,000 mg/m2	Busulfan
Dacarbazine	Clofarabine	Docetaxel	Cetuximab
Dactinomycin	Cyclophosphamide <1,500 mg/m2	Doxorubicin	Fludarabine
Mechlorethamine	Cytarabine>1,000 mg/m2	Etoposide	Pralatrexate
Streptozotocin	Daunorubicin	Gemcitabine	Rituximab
AC combination	Doxorubicin	Ixabepilone	Vinblastine
	Epirubicin	Methotrexate	Vincristine
	Idarubicin	Mitomycin	Vinorelbine
	Ifosfamide	Mitoxantrone	
	Irinotecan	Paclitaxel	
	Oxaliplatin	Panitumumab	
		Pemetrexed	
		Temsirolimus	
		Topotecan	
		Trastuzumab	

3.13 PHARMACOLOGICAL OPTIONS FOR PREVENTION/MANAGEMENTOF CCINV

Table 3.6: Dosing schedules of antiemetic drug according to chemotherapy risk are listed below(Basch, 2011)

Class/ Example(s)	Mechanism of Action	Uses	Side Effects
Corticosteroids ● Dexamethasone 10-20mg IV/PO pre-chemo, or 4mg PO q6h for layed N/V	Unknown; may inhibit prostaglandin synthesis in higher CNS centers	● Adjunct for moderate to highly emetogenic chemo ● For low to moderateemetogenic chemo ● Delayed N/V ● Breakthrough N/V	Hyperglycemia, insomnia, GI upset, delirium
5-HT3 receptor antagonists (RA)[a] ● Ondansetron (variable dose) ● Granisetron (2 mg PO, 10 mcg/kg IV) ● Palonsetron[b] 0.25mg IV Day 1	Blocks 5-HT3 receptors in GI tract, CNS	● Adjunct for moderate to highly emetogenic chemo ● Delayed N/V ● Breakthrough N/V	HA, constipation, QT prolongation (ondansetron only)
Substance P/NK RA[c] ● Aprepitant[d] 125mg PO Day 1,then 80mg PO Days 2-3 ● Fosaprepitant 150mg IV Day 1	Blocks human substance P/neurokinin-1 receptors	● Adjunct for moderateto highly emetogenic chemo	Fatigue, GI upset
Benzodiazepines	Acts at higher	● Anticipatory N/V	Sedation, antegrade

● Lorazepam 0.5-2mg IV/PO q4-6h	CNS centers	● Breakthrough N/V	amnesia
Phenothiazines ● Prochlorperazine 10mg IV q6h, or 10-30mg PO q6h, or 25mg PR q12h ● Promethazine 12.5-25mg IV/IM/PO/PR q4-6h	Blocks D2 receptors in CNS	● Minimal to low emetogenic chemo ● Breakthrough N/V	EPS, sedation, hypotension
Butyrophenones ● Haloperidol 1-4mg IV/IM/PO q6h	Blocks D2 receptors in CNS	● Breakthrough N/V	EPS, sedation, hypotension, QTprolongation
Substituted Benzamides ● Metoclopramide 10-40 mg PO/IV q4-6h	Low dose---promotility High dose---blocks D2 receptors in GI tract, CNS, and some 5-HT3 Receptors	● Minimal to low emetogenic chemo ● N/V associated with eating ● Breakthrough N/V	EPS, diarrhea, agitation, mild sedation
Antihistamines ● Benadryl 25-50mg IV/PO q4-6h	Blocks H2 receptors in vestibular center, vomiting center	● Adjunct agent ● Breakthrough N/V	Sedation, confusion, dry mouth, urinary retention, visualchanges
Anticholinergics ● Scopolamine 1 patch q72h	Blocks acetylcholine receptors in vestibular system, vomiting center	● Breakthrough N/V	Same as for antihistamines

Efficacy significantly improved when **a**) combined with steroids. **b)** 2nd generation 5-HT3 RA; 100-fold higher binding affinity for 5-HT3 receptor; T½ ~40h; as good as traditional 5-HT3 RAs for acute N/V, better for preventing delayed emesis. **c)** Substance P is member of tachykinin family of neuropeptides; biologic activity mediated by neurokinin (NK-1) receptor; substance P and NK-1 receptors located in brain, GI tract; thought to play role in acute and delayed CCINV. **d)** CYP3A4 inhibitor so lots of drug interactions

3.14 ROLE OF PSYCHOLOGICAL INTERVENTIONS:

This is presented under following headings.

a) Psycho physiologic dimensions of CCINV.

b) CAM therapies for CCINV.

c) Yoga and CCINV.

d) Jacobson's Progressive Muscle Relaxation and CCINV.

TABLE 3.7: literature review of psychological interventions in CCINV

Sl. No.	Author, year	Outcomes /Findings
1.	Hesketh PJ 2008	Despite recent advances in the understanding of chemotherapy induced nausea and emesis and development of new generation antiemetic agents, nausea and emesis continue to be the most feared distressing side effect of chemotherapy
2.	National comprehensive Cancer Network 2011.	The occurrence of nausea and emesis relative to chemotherapy administration can be classified as either acute (within first 24 hrs. with a peak of 5-6 hours), delayed (after 24 hours of administration) or anticipatory (nausea and emesis prior to subsequent doses of chemotherapy)

3.	Roscoe JA 2000	The incidence of nausea may actually have risen despite the reduction in the incidence of vomiting after the introduction of 5- HT3 receptor antagonists
4.	Grunberg SM 2004	Delayed nausea and emesis, which may appear even in the absence of acute nausea and emesis, remain important targets for improved therapeutic intervention.
5.	Grunberg SM 2013	Current antiemetic agents, such as 5-hydroxytryptamine-3 (5-HT3) antagonists and neurokinin-1 (NK-1) antagonists, have markedly decreased hospitalization for chemotherapy and have nearly eliminated acute emesis. The second-generation 5-HT3 receptor palonosetron has a unique pharmacology that makes it especially effective at preventing delayed emesis.
6.	Navari RM 2013	Olanzapine was significantly better than metoclopramide in the control of breakthrough emesis and nausea in patients receiving highly emetogenic chemotherapy
7.	Koeller JM 2013	Created three tables: emetic risk of chemotherapy; treatment options based on emetic category; and antiemetic dosing recommendations. Use of these tables should make appropriate antiemetic selection more straightforward and easier for the practitioner in an everyday setting.
8.	Cohen L 2007	CCINV remained a substantial problem for patients receiving chemotherapy in this community-based sample, especially delayed CCINV. CCINV significantly interfered with patient QOL and daily functioning.

9.	Glaus A 2004	CCINV remains a significant problem in routine practice, particularly in the delayed phase post treatment. Overall, CCINV had a negative impact on patients' daily life.
10.	Bonadonna G 1995	It has been reported that dose reduction due to toxicity has led to poorer survival when chemotherapy was given for a curative intent
11.	Bosly A 2008	Dose reductions and/or delays, mainly due to hematological toxicities, resulted in a reduction in treatment intensity. These data indicate that patient outcome is improved when the intensity of chemotherapy treatment is optimal
12.	Young A 2009	It has been reported that dose reduction due to toxicity has led to poorer survival when chemotherapy was given for a curative intent
13.	Vidall C 2011	Various guidelines the Multinational Association of Supportive Care in Cancer (MASCC) and National Cancer Care Network (NCCN) propose the use of 5HT3 receptor antagonists and NK1 receptor antagonists along with corticosteroids
14.	Molassiotis A, 2002	There is increased variability among patients on predisposition to CCINV with same metogenic potential due to several modifiable and non-modifiable host factors that increase risk for CCINV.
15.	De WR, Herrstedt J 2004	Despite following guidelines 50% of patients still experience delayed nausea.

16.	Kramer MS 2004	NK1 receptor antagonists act via central mechanisms in controlling acute nausea and emesis, substance P dependant central mechanisms have been purported to be behind occurrence of delayed nausea. These neurotransmitters have also been implicated in affective states such as anxiety and depression and their antagonists have shown to reduce these states subsequently.
17.	. Rupniak NM (2002)	Substance P and NK1 receptors are also intimately associated with ascending 5-HT and norepinephrine projections to the forebrain, and alterations in the function of these systems are also likely to be related to the antidepressant efficacy of SPAs.
18.	Orita K 2010	Substance P levels have been shown to be reduced by moderate exercise in animal models.
19.	Molassiotis A (2000)	PMRT is an effective adjuvant method to decrease nausea and vomiting in chemotherapy patients.
20.	Taneja I 2004	Increase in electro physiologically recorded gastric activity in the conventional intervention group and enhanced parasympathetic reactivity as measured by heart rate parameters, in yogic intervention group. The study indicates a beneficial effect of yogic intervention over conventional treatment in diarrhea-predominant IBS.
21.	Abell TL 2002	Most of the antiemetic agents have no effect on gastric motor function and some may delay gastric emptying exacerbating nausea.

22.	Kvale G 1991	Anticipatory symptoms are caused by anxiety that is known to affect basal ANS tone.
23.	Schwartz MD 1996	There is a special link between nausea and changes in affective response to food items. These results also highlight the unique opportunities for studying food aversion formation in the oncology setting.
24.	Raghavendra RM, 2008	Yoga on cancer patients have shown to reduce psychological distress.
25.	Vadiraja HS 2009	There was a significant positive correlation between physical and psychological distress and fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, and constipation but significant negative correlation between the activity level and fatigue, nausea and vomiting, pain, dyspnea, insomnia, and appetite loss.
26.	Raghavendra RM, 2009	Yoga on cancer patients have shown to reduce anxiety level.
27.	Cohen L 2004	Yoga on cancer patients have shown to improve sleep.
28.	Raghavendra RM 2007	Yoga on cancer patients have shown to reduce nausea and emesis.
29.	Buffart LM 2012	Yoga appeared to be a feasible intervention and beneficial effects on several physical and psychosocial symptoms were reported. In patients with breast cancer, effect size on functional well-being was small, and they were moderate to large for psychosocial outcomes.

30.	Harder H 2012	There is moderate to good evidence that yoga may be a useful practice for women recovering from breast cancer treatments. Large-scale RCTs using objective measures and patient-reported outcomes with long-term follow-up are needed to substantiate whether the benefits are true and sustainable.
31.	Zhang J 2012	Indication of how effective yoga might be when they were applied by women with breast cancer except for mildly effective in QOL improvement. The findings were based on a small body of evidence in which methodological quality was not high. Further well-designed RCTs with large sample size are needed to clarify the utility of yoga practice for this population.
32.	Tripathi NS 2012	Agni maximally represents digestive & metabolic fire in the body .It is the substance in the secretions of the body which are directly responsible for chemical changes in the body
33.	Whitley E 2002	How to calculate an ideal sample size is also discussed within the context of factors that affect power, and specific methods for the calculation of sample size are presented for two common scenarios, along with extensions to the simplest case.
34.	Martin AR 2003	Standardization of a modified FLIE
35.	Cohen S1 1991	Reliability of Perceived stress Scale
36.	Zigmond AS 1983	Validity of hospital anxiety and depression scale
37.	Bjelland I 2002	Validity of hospital anxiety and depression scale

38.	Vani and Prasad 2013	Āyurveda signifies its relevance with modern physiology of digestion and metabolism thus providing an extensive field of research and scientific status in the present scenario
39.	Parkman HP 2003	Patients with nausea, vomiting, or other dyspeptic symptoms exhibit EGG rhythm disturbances or blunting of meal-evoked EGG signal amplitude increases. These abnormalities correlate to some degree with delayed gastric emptying of solids. In selected patients, EGG may be complementary to gastric emptying testing. To date, no therapies have convincingly demonstrated in controlled studies that correcting abnormalities detected by EGG improves upper gastrointestinal symptoms. Proposed clinical indications for performance of EGG in patients with unexplained nausea, vomiting and dyspeptic symptoms must be validated by prospective controlled investigations.
40.	You CH 1980	With electrogastrography in a heterogeneous group of patients with unexplained nausea and vomiting a subgroup can be discerned with abnormal myoelectrical activity. Findings suggest that this abnormal myoelectrical activity is related to these symptoms.
41.	Agrawal AK (2010)	In regard of treatment, *Pitta* and *Agni* are the same, whereas in accordance to their, build they differ from each other.
42.	Divya K, Tripathi JS, Tiwari SK (2013)	Status of *Agni* in the body can be evaluated on the basis of specific signs & symptoms and in Āyurveda *Agni* is used to assess the overall effect of drug on body.

43.	Basch E 2011	Update Committee noted the importance of continued symptom monitoring throughout therapy. Clinicians underestimate the incidence of nausea, which is not as well controlled as emesis.
44.	Radhakantdev R, 1967	*Agnis*are descriptive categories that are responsible for carrying out the action of different enzymes and metabolic processes.
45.	Rubenstein EB 2006	Despite major advances, CCINV remains uncontrolled in some patients. Current efforts are focused on treating refractory emesis and include both the clinical evaluation of compounds marketed for other indications and the preclinical evaluation of novel molecules targeting other transmitters in the emetic pathway. Ongoing work in pharmacogenomics has postulated several candidate genes that could be involved in emetic sensitivity and responsiveness to antiemetic therapy. Investigations into the pharmaco-genomics of CCINV may someday be able to aid in the identification of high risk patients and patients unlikely to respond to conventional therapies.
46.	Metri K 2013	Combat serious chemo-radiotherapy related side effects through simple but effective home-based Āyurveda remedies. The remedies described are commonly available and safe. These simple Āyurveda based solutions may act as an important adjuvant to chemo-radiotherapy and enhance the quality of life of cancer patients.
47.	Vempati RP 2002	Sympathetic activity decreased after guided relaxation based on yoga, depending on the baseline levels.

48.	Trotti A 2003	A comprehensive grading system for the adverse effects of cancer treatment.
49.	Amruthesh S 2007	Agni becomes weak (mandāgni), a number of unwanted unripe by-products of digestion and metabolism start forming and accumulating in the body at different levels from the gross to the molecular level, from a local gastrointestinal tract (GIT) level to the systemic level in tissues and cells. Such products are collectively called ama and act as toxic and antigenic materials, giving rise to many antibodies.
50.	Miller AD 1994	AP is excited by systemic administration of emetic drugs. Activation of the AP probably leads to nausea and vomiting through its projection to the neighbouring NTS. The NTS may serve as the beginning of a final common pathway by which different emetic inputs trigger vomiting.
51.	Messick, S. 1980	Test validity and the ethics of assessment.
52.	KiranR, 1989	Development of a coping checklist.
53.	Dodd MJ, 2001	Side effects are seen as symptom clusters.
54.	Dodd MJ, 2004	Concept of symptom clusters.
55.	Vranda. .M.N 2009	Phases of Scale Development.
56.	CCRAS 1987	There is no fundamental difference in physical and biological fire or Agni, except that the latter is associated with living organism – a monograph based on fundamental aspects of Āyurveda.
57.	Bhagawan D, 1993	A new mode of approach to the basic aspects of Āyurveda

The present study is intended to assess the mechanism of action of yoga intervention in managing chemotherapy induced nausea and emesis in cancer patients receiving Highly/Moderately emetogenic chemotherapy regimens.

Chapter-4

AIMS AND OBJECTIVES

4.1 AIMS

The aim of the present study is to evaluate the effects of an integrated yoga program on jāṭarāgni and associated symptoms clusters of the Gastro Intestinal Tract along with autonomic, psychological and psychosocial factors in cancer patients with solid malignancies and lymphomas, receiving highly or moderately emetogenic chemotherapy.

4.2 OBJECTIVES

4.2.1 General Objectives

The objective of the study was to develop and standardize a checklist to assess cancer chemotherapy induced Jāṭharāgni impairment that relies on gastrointestinal (GI) symptoms described by Āyurveda. Once such an instrument was made available, it was envisaged to use it to assess the effect of yoga therapy for CCINV in patients undergoing chemotherapy.

The present study also attempted to evaluate the effects of a Yoga based intervention in patients undergoing conventional treatment on appetite reduction, cardiac and gastric autonomic functioning, stress, anxiety, depression, and quality of life by way of conducting a three arm randomized control trial.

4.2.2 Specific Objectives

1. To understand the concept of Jāṭharāgni according to Āyurveda and Yoga texts in reference to cancer chemotherapy induced nausea and vomiting.

2. To develop and standardize a checklist to assess Jāṭharāgni impairment in patients with solid malignancies and lymphomas experiencing chemotherapy induced nausea and vomiting.

3. To conduct a randomized control trial, evaluating the effects of an integrated yoga module on Jāṭharāgni impairment in cancer patients undergoing chemotherapy.

4. To correlate changes in Jāṭharāgni impairment with autonomic and psychosocial variables.

4.3 RESEARCH QUESTIONS

1. Can a standardized checklist be developed, for cancer patients undergoing Chemotherapy, to determine the extent of impairment in Jāṭharāgni that is based on description of gastric symptomatology in Āyurveda

2. Can holistic system of healing like yoga effect Jāṭharāgni?

3. Can yoga improve health and psychological indices of cancer patients experiencing CCINV?

4.4 HYPOTHESIS

1. Yoga and Jacobson's PMRT effect jāṭarāgni impairment in cancer patients undergoing chemotherapy.
2. Yoga and Jacobson's Progressive muscle relaxation Technique (PMRT) are able to effect CCINV and associated autonomic and psychological functioning in cancer patients undergoing chemotherapy.

4.4.1 Null Hypothesis

1. Neither Yoga nor Jacobson's PMRT may effect Jāṭharāgni Impairment in cancer patients undergoing chemotherapy.

2. Neither Yoga nor Jacobson's PMRT would affect CCINV and associated autonomic and psychological functioning in cancer patients undergoing chemotherapy.

4.5 RELEVANCE AND BENEFITS OF THIS STUDY

The gastro-intestinal (GI) disturbances that are a result of chemotherapy are severely debilitating to cancer patients and are not given adequate attention, due to its subjective and transitional nature. There is an urgent need to address nausea and vomiting in these populations as these are the most common and distressing symptoms and there is substantial disparity between the treating guidelines and clinical practice. Modern medical science suggests that patients experience a cluster of GI symptoms during chemotherapy, while traditional healing systems like Āyurveda and yoga describe in greater detail, the aetiology, physiology and remedies for nausea and vomiting. Thus a holistic understanding and an instrument that may measure GI disturbance that is based on Āyurveda and Yoga knowledge is necessary for CCINV patients. Yoga, an ancient system of restoring health, added onto conventional medicine, may be the key to a holistic approach in dealing with chemotherapy induced GI disturbances. The study describes the development and standardization of a checklist that is able to detect and evaluate jāṭarāgni Impairment through the assessment of GI symptomatology as described in Āyurveda texts. The Jāṭharāgni Impairment Checklist (JIC) helps in clinical evaluation of the severity of the GI related adverse effects and helps in intervening with suitable lifestyle, dietary or pharmacological measures to manage

CCINV. Jāṭarāgni, being described as a subtle form of digestive energy is difficult to describe directly and hence understanding its effects on GI symptoms forms a good way of assessing the GI side effects of chemotherapy.

Chapter-5

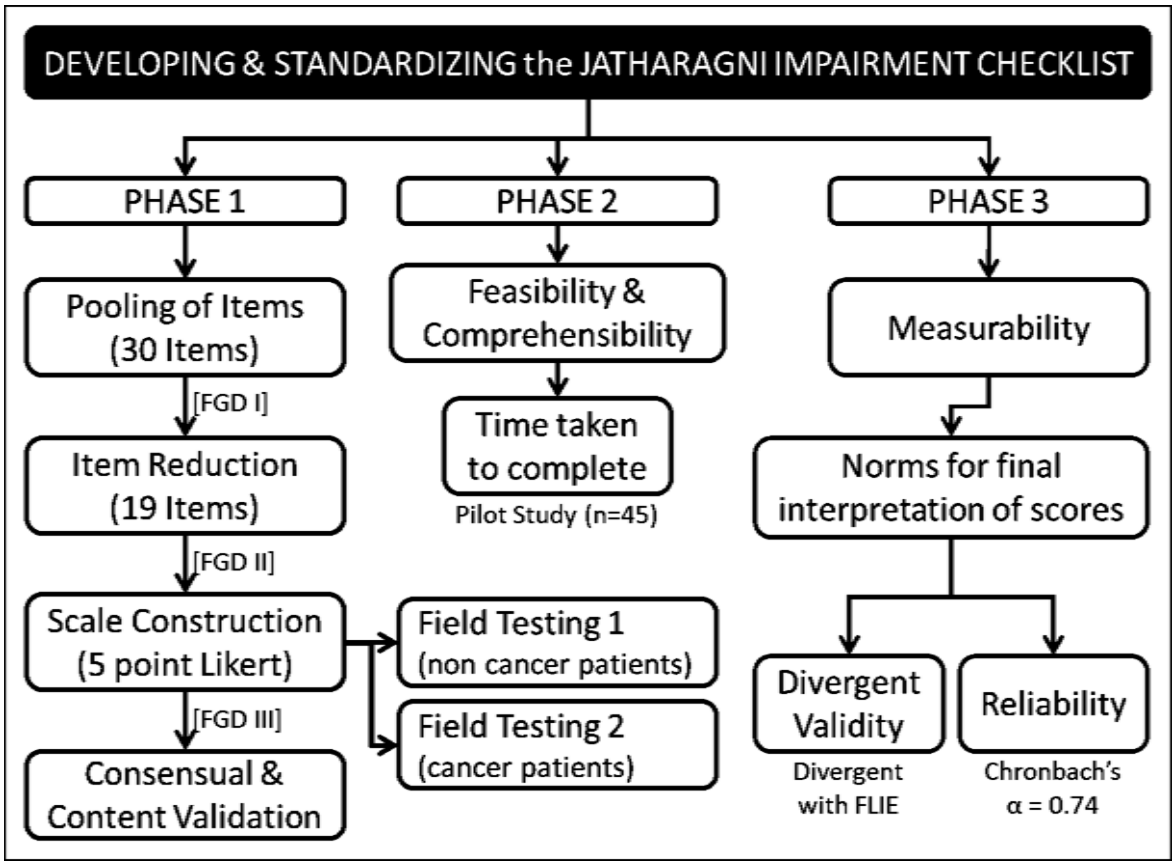
MATERIALS AND METHODS

This chapter presents the details of the procedures involved in executing the project. It is divided into two studies as follows.

5.1 STUDY 1:DEVELOPMENTS AND STANDARDIZATION OF JĀṬHARĀGNIIMPAIRMENT CHECKLIST (JIC)

The figure below provides an overview of all the steps involved in the development and standardization of the Jāṭarāgni Impairment Checklist. The present methods used in this study follow previous standard scale development procedure (Vranda-2009and Dr KiranRao).The individual steps are comprehensively described in sections below.

Fig. 5.1: developing& standardizing the jāṭharāgni impairment checklist



5.1.1 Phase- 1

5.1.1.1 Pooling of items

The first step in development of a scale involves the identification and the creation of the pool of the universe of items. As part of generating the universe of items, the researcher contacted thirty different Āyurveda experts, explained the rationale of the study and documented their views on Agni with respect to its various functionalities and manifestations. Experts suggested that evaluation of Jāṭharāgni and its impairment could be possible by the observation of the symptoms of Jāṭharāgni impairment as the checklist was being developed for patients with CCINV. A total of 30 symptoms were listed that could be indicative of an impaired Jāṭarāgni. References for these symptoms were collected from Āyurveda texts like Caraka saṁhita, Suśruta saṁhita, Mādhavanidāna Aṣṭāṅga hridaya, Aṣṭāṅga Saṅgrahaand other textbooks (Bhagwan Dash 1993) Common Chemotherapy side effects and cancer symptoms were also referred as per Common terminology Criteria for Adverse Events (CTCAE version 3). The original Sanskrit phrases, their meanings in English were compiled as a master-list. Thus, thirty original Sanskrit symptoms on Jāṭarāgni impairment formed the initial item pool of JIC.

5.1.1.2 Item reduction

The first Focus Group Discussion (FGD – 1) was organized in order to minimize the number of items in the JIC. The researcher conducted the FGD with a team of 10 Āyurveda experts for proving their inputs on whether to remove or include items based on its appropriateness. The researcher posed each of the symptoms to the group of experts and the items that were completely agreed upon by five or more judges were

retained in the checklist. The reason for removing an item was explored through the FGD. Overlapping, repeated, irrelevant ambiguous or vague items were eliminated. Thus a total of nineteen symptoms formed the checklist after having eliminated eleven items.

5.1.1.3 Scale construction:

The scale was constructed keeping in mind the criteria for uniformity in scoring. A Likert (Zyzanskiet al. 1974) scale with four options (none, mild, moderate and severe) was chosen as possible responses. After considering different bias of scale construction, the experts also confirmed that the items of the checklist were linguistically equivalent (Sanskrit terms were translated to English).

A second FGD (FGD – 2) was conducted where the researcher posed each of the 19 symptoms to the group comprising five oncologists to conform the appropriateness of items. Those items that received three or more votes were retained in the checklist. They suggested that the symptom checklist be modelled based on Common Terminology Criteria for Adverse Events (CTCAE Version 3.0). The updated checklist was administered to both non cancer patients taking Āyurveda treatment (n=10), from Āyurveda College, and those with cancer on chemotherapy (n=10) from Health Care Global Hospital, as part of the two field tests being conducted for confirming the measurability of the checklist. It was seen that the checklist was able to detect differences in the level of Jāṭarāgni impairment before and after pañcakarma treatment in the non-cancer group while majority of patients had a zero score for nausea and vomiting items at baseline before chemotherapy in the cancer group. A verbal consent was elicited prior to their involvement in the field test protocol and confidentiality of subjects was maintained.

5.1.1.4 Consensual and content validity

As part of establishing the consensual and content validity of the scale, a third FGD (FGD-3) was conducted. The FGD convened 17 members with different expertise (Āyurveda, oncology, yoga and clinical psychology). The experts were asked to provide their opinion for each of the items with regard to cultural relevance, clarity and ease of comprehension, readability and suitability. Those items which were agreed upon by nine or more judges confirmed validity and were retained in the checklist. 6 items did not satisfy the criteria and were dropped from the checklist resulting in a 13 item checklist. Experts also provided some suggestions as listed below.

- For improving the clarity of reporting, it was suggested that an alternate rating be used that was more descriptive of the symptom. This is in line with the CTCAE 3.0
- To capture symptoms other than Nausea and Vomiting to prove divergent validity.
- It was suggested that along with the responses, a visual analogue scale to evaluate the time interval between each meal and quantity taken at each meal was to be included.

5.1.2 Phase-2

5.1.2.1 Pilot Study

Subjects for pilot study were chosen from 15 subjects (5 from each group), randomly selected from the first 60 subjects to enrol into the randomised controlled trial that is explained in the later part of this thesis, conducted at Health Care Global (HCG) Bangalore. Pilot study was carried out with 13 items of checklist.

The aim was to assess the feasibility and comprehensibility of checklist. This self-reported checklist was found to be readable and comprehendible and was able to capture the difference in the Jāṭarāgni impairment level before and after chemotherapy. The time taken to complete the checklist was found to be about 10 minutes. The visual analogue scale for frequency of meals taken was not understood by the subjects and thus dropped from the checklist.

5.1.3 Phase-3

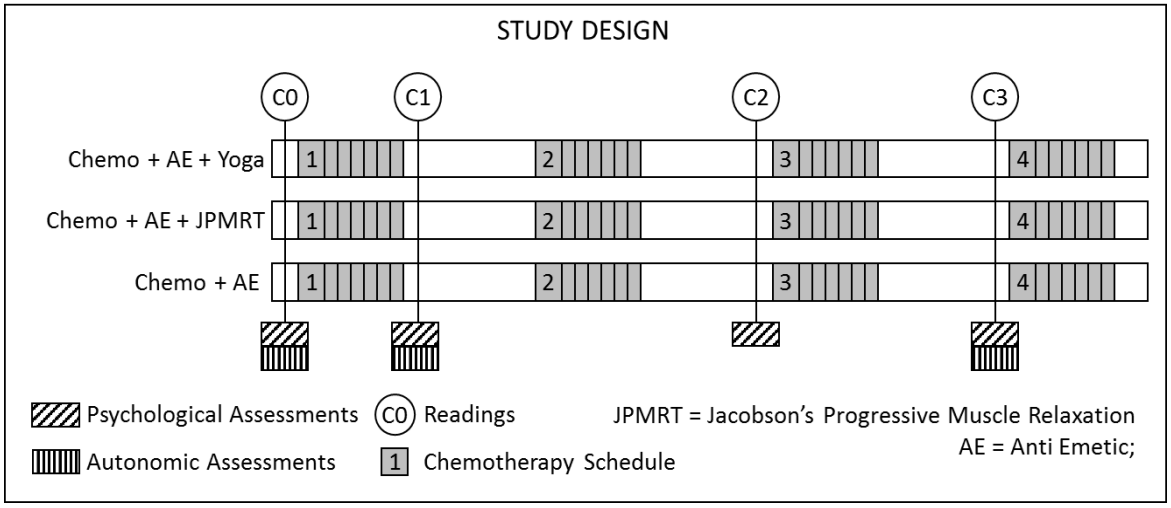
The third phase examined the measurability of the checklist, established the norms for interpretation and also calculated the reliability and validity of the Jāṭarāgni Impairment Checklist. This was done as part of the three arm randomized control trial where baseline data for all the subjects in the RCT was used to achieve the objectives of Phase – 3. Divergent validity was established by comparing the JIC with the Functional Living Index of Emesis (FLIE). The detailed material and methods of the RCT has been provided in further sections.

5.2 STUDY 2–RANDOMIZED CONTROL TRIAL ON THE EFFECTS OF YOGA ON CCINV

5.2.1 Design

This study was a prospective three arm randomized control trial involving cancer patients undergoing chemotherapy. While all three arms received chemotherapy and standard anti-emetic treatment, one group also received yoga, the second group received Jacobson's Progressive Muscle Relaxation (JPMRT) and the third served as a Control (Waitlist). A figure depicting the study design is given below.

Fig. 5.2: Study design



5.2.1.1 Setting

The study was carried out at Health Care Global (HCG) Cancer Hospital situated in Bengaluru.

5.2.1.2 Sample Source

Patients, who enrolled for chemotherapy over 16 months between January 2011 to April 2012 were screened and those who satisfied the selection criteria were enrolled into the study.

5.2.1.3 Sampling and allocation technique

A convenient sample was obtained of those who registered for chemotherapy at the above mentioned hospital. Subjects were allocated into one of three groups using sealed opaque envelopes with group assignments. Random numbers were generated using computer software available at www.randomizer.orgfor 3 group assignment.

5.2.1.4 Sample Size

After the initial screening, 40 subjects were allocated into each arm based on (standardized effect size with yoga intervention vs. supportive therapy as 0.69 for

nausea frequency and 0.95 for nausea intensity (Raghavendraet al. 2006). Average estimates of the two effect sizes were0.82. Considering *p* at 0.05 and 80% power, the $C_{p,}$ power value was 7.9. Going by the formula we had n= 3 / 0.82 ^{2} x 7.9 = 36 subjects in each arm. Considering and attrition of 10% (3 subjects) we recruited approximately 40 subjects in each arm).

5.2.1.5 Research Ethics and Trial Registration

This study was approved by the institutional ethics committees of HCG Private. Limited.[Y010810]. Written informed consent was taken from all subjects prior to their participation. No invasive procedures were conducted as part of this study. The study was registered [NCT 01387841]

5.2.2 Selection Criteria

The selection of participants was based on the below criteria. Only subjects, who satisfied every criterion below, were eligible and were included in the study.

Inclusion Criteria	Exclusion Criteria
1. Solid malignancies and lymphomas 2. Receiving Highly or Moderately Emetogenic Chemotherapy 3. Between 18-70 years 4. Chemotherapy naïve 5. Ability to read and write English or Kannada. 6. Eastern cooperative oncology group(ECOG) performance status ≤2	1. Brain metastases 2. Concurrent medical condition likely to influence survival, affect the study assessments or intervention, interfere with nausea/vomiting response a. Severe renal or hepatic impairment b. Uncontrolled diabetes and hypertension c. GI malignancies, ascitis, uraemia d. Neurological disorders (Parkinson's disease, myotonic dystrophy etc.) e. GI obstructions f. Cognitive impairments. 3. History of abdominal surgeries in the last 3 months 4. Regular participation in a behavioral intervention/yoga in the last 6 months.

	5. Surgeries <3 weeks prior to randomization 6. Acute unresolved toxicities
The selection criteria were designed to include as many subjects as possible into the study while excluding factors that could confound EGG signals (3-6), interfere with treatment (1-2), or confound results (1, 7, 8).	

5.2.2.1 Screening and Recruitment

Subjects consenting to participate in the study and satisfying the selection criteria were randomized to receive either yoga with antiemetic support, progressive muscle relaxation with antiemetic support and antiemetic support only before their first cycle of chemotherapy.

After taking detailed clinical histories prior to admission for 1st chemotherapy cycle (C0), subjects were provided questionnaires for Jāṭarāgni impairment, mood states, perceived stress, and quality of life and were evaluated for cardiac and gastric autonomic status. Then they were randomized to receive either of the intervention 1 hour prior to chemotherapy infusion. Subjects in JPMRT group and yoga group were asked to practice their respective interventions twice daily for the following 6 days and maintain a dairy noting nausea and emesis frequency and severity and medication intake every day. From there on subjects were asked to practice the intervention at least once every day for next 3 cycles of chemotherapy. Psychological, gastric and autonomic parameters were assessed on the 6th day (C1) and again before the second infusion (Day 21) (C2). Subjects were monitored for compliance to their respective interventions for next 3 cycles and evaluated again for the same before the 4th cycle of chemotherapy (C3). The Control (Waitlist) group were provided with an option to join either intervention groups after they had provided their data for C3.

5.2.2.2 Chemotherapy regimen

All subjects in this study received highly or moderately emetogenic chemotherapy schedule during the course of their chemotherapy as per the American Society of Clinical Oncology (ASCO Guidelines). The chemotherapy schedule and the cycle duration were decided by the Oncologists at the study start. Patients also were prescribed anti-emetogenic medication during the course of chemotherapy.

5.2.3 Intervention

5.2.3.1 Yoga group

The yoga intervention consisted of a series of āsana (postures), breathing exercises, regulated nostril breathing (praṇāyāma) and relaxation techniques (Quick Relaxation Technique) for 25 minutes. The sequence of the yoga intervention is given below.

Table 5.1: Sequence of yoga module for intervention (Duration – 25minutes)

Āsana	**Position**	**Duration**
Śavāsana: Relaxation with breath awareness (Quick relaxation technique)	Supine	3 minutes
Uttanapādāsana: Supine straight leg raising (Alternate legs followed by both legs)	Supine	3 minutes
Pavanamuktāsana: (Knee to chest position)	Supine	2 minutes
Śavāsana: Relaxation with breath awareness (Chanting a monosyllable "A")	Prone	2minutes
Bhujaṅgāsana: Cobra pose	Prone	2 minutes
Śalabāsana: Locust pose	Prone	2 minutes

Makarāsana: Crocodile pose (Chanting monosyllable "U")	Prone	2 minutes
Vajrāsana- Diamond Pose	Sitting	2 minutes
Śashankāsana- Rabbit pose (Chanting monosyllable "M")	Sitting	2 minutes
Śavasana: Relaxation with breath awareness (Awareness on abdominal and chest movements)	Supine	5 minutes

5.2.3.2 Jacobson's Progressive Muscle Relaxation Technique

The JPMRT group followed the technique designed by Jacobson which involves tightening of different muscle groups of the body and then sequential relaxing, lasting for 25 minutes. Below is a list of steps involved in the JPMRT.

Table 5.2: **Sequence of Jacobson's relaxation module for intervention (Duration – 25minutes)**

Hands: Fists are held tightly (tensed) and relaxed. Then, the fingers are extended and relaxed.
Biceps and triceps: The biceps are tightened such that the fist is not tensed and relaxed. Then the triceps are relaxed by extending the arm and relaxed.
Shoulders: The shoulders are pulled backward and relaxed. Likewise, push the shoulders forward making a hunch and relax.
Neck (Lateral): The shoulders are relaxed and the head is slowly turned towards right side as far as possible and relaxed. Similarly its turned towards left side and relaxed.
Neck (forward): Neck is bent forward such that chin touch into the chest and relaxed. Backward bending of neck is not recommended.

The mouth is opened as wide as possible and relaxed. The lips are pursed tightly and relaxed.
Tongue (extended and retracted): Mouth is opened widely and tongue extended out and relaxed on the floor of the mouth. Then tongue retracted inwards into the throat and relaxed.
Tongue (roof and floor): Tongue extended towards the roof of the mouth touching the palate and relaxed. Tongue is extended downward into the bottom of mouth and relaxed.
Eyes: Eyes opened widely making furrows on the brow and relaxed. Eyes are closed tightly and relaxed. Simultaneously the eyes, forehead and nose are relaxed after each tensing.
Back: Body pushed forward such that the back is arched and relaxed. The shoulder should be relaxed while practicing the same. One should be cautious while practicing the same.
Butt: The butt is tensed tightly and pelvis is raised of the floor and relaxed.
Thighs: The legs are raised to about six inches off the floor without tensing the stomach and relaxed. The heels are then pressed against the floor and relaxed.
Stomach: The stomach is pulled inward as much as possible and relaxed. Consequently the stomach is pushed outward and relaxed.
Calves and feet: The Feet is extended forwards and relaxed without raising the legs. Feet are pointed upward as far as possible and relaxed. One needs to be cautious of cramps. (The feet have to be shaken and loosened if cramps are experienced).
Toes: Toes bent forward and relaxed. Toes bent upward as much as possible and relaxed. Note: Jacobson's relaxation technique can be done while lying supine or resting on a chair.

5.2.3.3 Control (Waitlist)

Control group received only counselling about the role of stress and mind in CCINV.

5.2.4 Outcome Measures

5.2.4.1 Primary outcome variable

a)JāṭarāgniImpairment Checklist

Involves measure for capturing GI disturbances (Jāṭharāgni impairment) using JIC. JIC is a thirteen symptom self-report check list used for measuring patients" Jāṭharāgni impairment level during cancer treatment Subjects were evaluated with the self-report JIC as a reliable and valid checklist with Cronbachs alpha=0.74 (Nandini et al 2014) --- Patients were asked to rate on a four point scale – None, mild, moderate and severe. JIC is used both during acute and delayed phase of CCINV with a 24 hour recall period and four day recall period respectively**.**

b) Visual Analogue Scale for Quantity of Meal

Used for assessing Quantity of meal taken by the patients. Subjects were asked to mark the level of reduction in food quantity on a ten-point meter scale. (0 value indicating 100% reduction and 10 indicating no reduction)

5.2.4.2 Secondary Variables

a) Functional Living Index Emesis

The Functional Living Index-Emesis (FLIE), an emesis- and nausea-specific quality-of-life (Qol) questionnaire for assessing impact of nausea and emesis on quality of life. It is used to measure both acute and delayed nausea and emesis following chemotherapy.

This has been validated in earlier studies and has shown excellent internal consistency reliability within the FLIE nausea and vomiting domains (Cronbach's alpha range: 0.75 to 0.78) (Martin AR, Pearson JD et al. 2003).

b) State Anxiety

State Trait Anxiety Inventory (STAI) is a self-report scale for measuring state anxiety and trait anxiety. This scale has twenty statements with a concurrent validity ranging from 0.75 to 0.80 with other tests. The A-state scale asks the subjects to indicate how they feel at a particular moment in time. Coefficient alpha reliabilities for the state measure range from 0.86 to 0.92. (Spielberger et al. 1970).

c) Perceived stress Scale:

The PSS is a ten-question scale that is commonly used to measure perceived stress or the level at which individuals view their current life situations as stressful. Reliability (internal reliability) of the PSS instrument is very strong, ranging from .84 to .86, and validity ranging from .31 to .76, when correlated with measures of physical and depressive symptoms. (Cohen S and Williamson. 1988.).

d) Hospital Anxiety and Depression Scale:

Participants self-report anxiety was assessed using hospital anxiety and depression questionnaire (Zigmond AS and . 1983). This scale has been developed to detect anxiety and depression in medically ill populations and has a strong reliability and validity with other scales and DSM III criteria. The reliability of HADS –A scale ranges from 0.63 to 0.90 across studies (Bjelland et al. 2002.).

e) Cardiac autonomic function

The basal cardiac autonomic status will be evaluated using heart rate variability which gives us a measure of sympathetic or parasympathetic dominance. The Electrocardiogram (ECG) was recorded for 5 min before water intake and 20 min after using Ag/AgCl solid adhesive pre-gelled electrodes (3M). The ECG was acquired using an ambulatory ECG system (AD Instruments) at a sampling rate of 1024 Hz and will be stored for off line analysis. The data was analysed with an advanced HRV analysis software program (LAB CHART PRO) inbuilt in the system.

f) Gastric autonomic function

Surface Electrogastrogram was assessed using an AD Instruments polygraph with EGG amplifier. In humans the normal frequency is (2.75- 3.75) or 3 cycles per minute (cpm). Bradygastria is an abnormally low frequency (1.0 -2.75 cpm) and tachygastria is abnormally high frequency (3.75-10.0 cpm). This test is recorded for 15 minutes in fasting and twenty minutes after a 250 ml water load test. (Parkman HP, Hasler WL et al. 2003). ECG recording:

5.2.5 Data Collection and Analysis

All the above measures were recorded at baseline (C0) and one the 6th day of the 1st cycle of Chemotherapy (C1) and for next 3 cycles respectively (C2, C3). Jāṭharāgniimpairment, Nausea Vomiting episodes, quality of life and psychological states were analysed using self-report questionnaires filled by participants. The data entry and scoring were done by personnel not involved in the study and not having knowledge of the allocation. Neuro-physiological data were recorded using the same

instrument under similar rest conditions for all participants. These data were blinded and interpreted by neurophysiologists in a collaborating institute.

Data were analysed using SPSS 16 for windows. Data were analysed using repeated measures ANOVA with post hoc Bonferroni correction. Both within groups and group by time effects were observed. For ordinal variables in quantity of each meal Pearson's correlation coefficient 'r' was used.

Chapter-6

RESULTS

6.1 STUDY 1: STANDARDIZATION OF CHECKLIST

There was strong reliability for JIC to measure impairment in Jaṭharāgni. The results suggest that this questionnaire captures subtleties of symptoms that need not individually impair GI function but can collectively increase distress. These symptoms mentioned are subjective and similar to the concept of symptom clusters proposed by Dodd et al. The JIC is an instrument for capturing GI disturbances. JIC is a self-report check list eliciting information of thirteen symptoms used for measuring patients' Jāṭarāgni impairment level during cancer treatment. Patients are asked to rate on a four point scale based on symptom severity. JIC may be used both during acute and delayed phase of CCINV with a 24 hour recall period and four day recall period respectively**.** In our pilot study on subjects with mean age of 49.3 ± 11.3 years JIC was shown to be a reliable and valid checklist (Nandini et al. 2014).

6.1.1 Reliability

The reliability of 13 item JIC was good with Cronbach's alpha=0.74 and inter-rater reliability between three raters varied between 0.68 to 0.80

6.1.2 Validity

Good divergent validity of JIC with FLIE indicating that it captured items that were not captured in the FLIE. The kappa values ranged between 0.01 to 0.09, across four cycles of chemotherapy in the overall study sample, indicating divergent validity. Values within each group also showed similar divergent validity compared to overall study sample indicating that intervention did not influence validity of the scale. This strong validity demonstrates the robustness of the scale to capture Jāṭharāgni symptoms

independent of FLIE (See table 6.1&6.2). The evidence of content validity has already been established in the initial phase.

Table 6.1: Divergent validity of Jaṭharāgni checklist with FLIE

Time Point	n	JIC vs FLIE		K	p-value
		Similar	Dissimilar		
		No (%)	No (%)		
C0	120	45 (37.5)	75 (62.5)	- *	-
C1	112	57 (50.9)	55 (49.2)	0.064	0.318
C2	104	45 (43.3)	59 (56.7)	0.019	0.769
C3	94	48 (51.1)	46 (48.9)	0.097	0.097
K value not calculated as FLIE at C0 was 0 for all items					

6.1.3 Symptom severity

Symptoms were graded based on their presence (subjective/clinical) and interference with GI function. Anorexia, taste alteration and dry mouth were some of the major symptoms that interfered with GI function. Though most of these symptoms were reported by patients many of them did not interfere with GI function (See Table 6.2 &.3).

Table 6.2: Severity of symptoms in JIC

Cycle	N	Mild (1) No (%)	Moderate (2) No (%)	Severe (3) No (%)
C0	120	45 (37.5)	38 (31.7)	37(30.7)
C1	120	43(35.9)	38 (31.6)	39 (32.5)
C2	109	41 (37.6)	46 (42.2)	22 (20)
C3	102	39 (38.2)	32 (31.3)	31 (30.4)

Table 6.3: Severity of individual symptoms in Jāṭharāgni checklist

Symptoms	Time Point	None (0)	Mild (1)	Moderate (2)	Severe (3)
Anorexia	C1	41 (37)	45(40)	22(20)	3 (3)
	C2	74 (69.2)	21 (19.6)	10 (9.3)	2 (1.9)
	C3	61 (61.0)	25 (25.0)	11 (11.0)	3(3.0)
Constipation	C1	75 (68)	28 (25)	7 (6)	1(1)
	C2	91 (85.0)	14 (13.1)	2 (1.9)	-
	C3	81 (81.0)	16 (16.0)	2 (2.0)	1 (1.0)
Diarrhea	C1	87(78.4)	19 (17.1)	4 (3.6)	1 (0.9)
	C2	100 (93.5)	6 (5.6)	1 (0.9)	-
	C3	90 (90.0)	9 (9.0)	1 (1.0)	-
Distention	C1	75 (67.6)	29 (26.1)	5 (4.5)	2 (1.8)
	C2	96 (89.7)	9 (8.4)	2 (1.9)	-
	C3	80 (80.8)	14 (14.1)	4 (4.0)	1 (1.0)
Dry Mouth	C1	48 (43.2)	51(45.9)	11(9.9)	1(0.9)
	C2	63 (58.9)	31 (29.0)	12 (11.2)	1 (0.9)
	C3	56 (56.0)	38 (38.0)	5 (5.0)	1 (1.0)
Flatulence	C1	79 (71.2)	23 (20.7)	8 (7.2)	1 (0.9)
	C2	89 (84.0)	11 (10.4)	6 (5.7)	-
	C3	72 (72.0)	24 (24.0)	4 (4.0)	-
Heartburn	C1	71 (64.0)	31 (27.9)	7 (6.3)	2((1.8)
	C2	93 (86.9)	10 (9.3)	4 (3.7)	-
	C3	78 (78.8)	17 (17.2)	4 (4.0)	
Taste	C1	40 (36.0)	46 (41.4)	24 (21.6)	1 (0.9)

alteration	C2	55 (51.4)	39 (36.4)	13 (12.1)	-
	C3	37 (37.0)	37 (37.0)	25 (25.0)	1 (1.0)
Heaviness	C1	75 (67.6)	28 (25.2)	8 (7.2)	-
	C2	93 (86.9)	10 (9.3)	3 (2.8)	1 (0.9)
	C3	80 (80.0)	17 (17.0)	3 (3.0)	-
Gurgling	C1	81 (73.0)	28 (25.2)	2 (1.8)	-
	C2	96 (90.6)	9 (8.5)	1 (0.9)	-
	C3	81 (81.0)	17 (17.0)	2 (2.0)	-
Eructation	C1	74 (66.7)	31 (27.9)	5 (4.5)	1 (0.9)
	C2	88 (83.0)	17 (16.0)	1 (0.9	-
	C3	82 (82.0)	14 14.0)	4 (4.0)	-
Excess salivation	C1	92 (82.9)	16 (14.4)	2 (1.8)	1 (0.9)
	C2	101 (94.4)	5 (4.7)	1 (0.9)	-
	C3	84 (84.0)	13 (13.0)	3 (3.0)	-
Quantity at each meal	C1	35 (31.5)	37 (33.3)	23 (20.7)	16 (14.4)
	C2	51 (47.7)	36 (33.6)	16 (15.0)	4 (3.7)
	C3	39 (39.0)	38 (38.0)	15 (15.0)	8 (8.0)

6.1.4 Cut- off Values

The 33rd percentile cut off scores was 2 (mean across all chemo cycles) and 66th percentile cut off was 6 (mean across all chemo cycles) in this study for in Jaṭharāgni impairment checklist.

6.1.5 Convergent Validity

Quantity of meal is an extrapolation of Agni quality as per ancient texts. We compared the convergent validity of all items on JIC with quantity of meal at chemotherapy cycle. There was a strong correlation on Spearmans rank correlation at different chemotherapy cycles of total Agni of JIC with quantity of each meal (All p's=0.001).

Table 6.4: Spearmans rank correlation between total Agni with quantity of each meal at different chemotherapy cycles.

Table 6.4: Quantity of each meal at various chemotherapy cycles

		N	Total Agni			
			C0	**C1**	**C2**	**C3**
Reduction in Quantity at each meal	C0	116	.619**			
	C1	111		.674**		
	C2	107			.673**	
	C3	100				.641**
**p<0.01, using Spearman's rank correlation						

6.2 STUDY 2: RANDOMIZED CONTROL TRIAL ON THE EFFECTS OF YOGA ON CCINV

6.2.1 Primary Outcome Variables

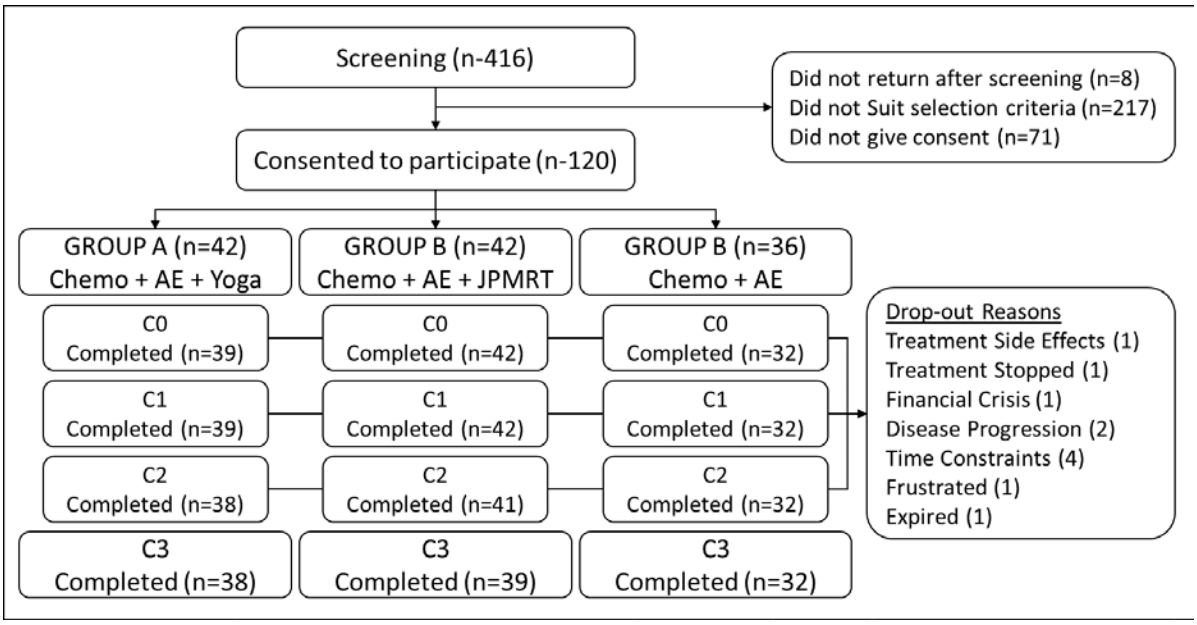
6.2.1.1 Socio-demographic data

The mean age of study sample was 49.3 ± 11.3 years. The distribution of gender, religious class, cancer type, grade, prior surgery and co-morbid illness was not significantly different between groups on chi square test of proportions.

6.2.1.1.1 Trial profile

Out of the total four hundred and sixteen screened patients, 191 were found eligible and 217 were not eligible for the study. Of the eligible 120 participated and 71 [37.2%] refused to participate citing various reasons and 8 did not turn up for treatment at the cancer center. The primary reasons for refusal were analysed. The primary reasons for refusing to participate in the research study was lack of belief in yoga [29.2%], fear that yoga postures would do harm during chemotherapy [2.8%], not able to do yoga due to fatigue and distress [8.3%], belief that they cannot or would not be able to perform yoga [6.9%], religious beliefs that yoga was associated with Hinduism [12.5%], Time constraints to attend classes or perform at home [13.9%], Noncompliance to data visits [18.1%], fear that participation in trial would breach privacy and confidentiality [6.9%], other co-morbid illnesses that prevented participation [1.4%].

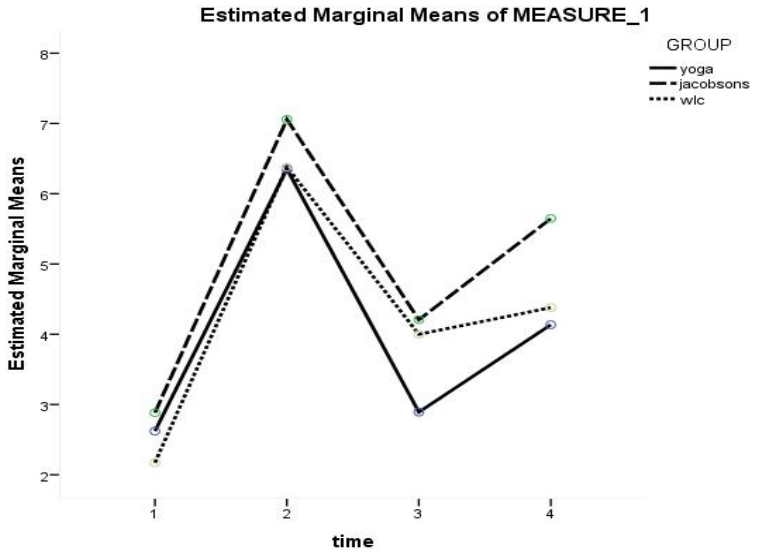
Fig 6.1: Trial Profile



6.2.1.2 Jaṭharāgni Impairment Checklist

In all the 3 groups between subjects effect was not significant for changes in total Agni score following 3 consecutive chemotherapy cycles F(2,97)=1.19, p=0.31. However within subjects effects was significant for time F (3, 97) =23.2, P<0.001 only. There was no significant group by time interaction effects (See Fig1).

Fig. 6.2.Group by time interaction effects on impairment in Agni during various chemotherapy cycles.



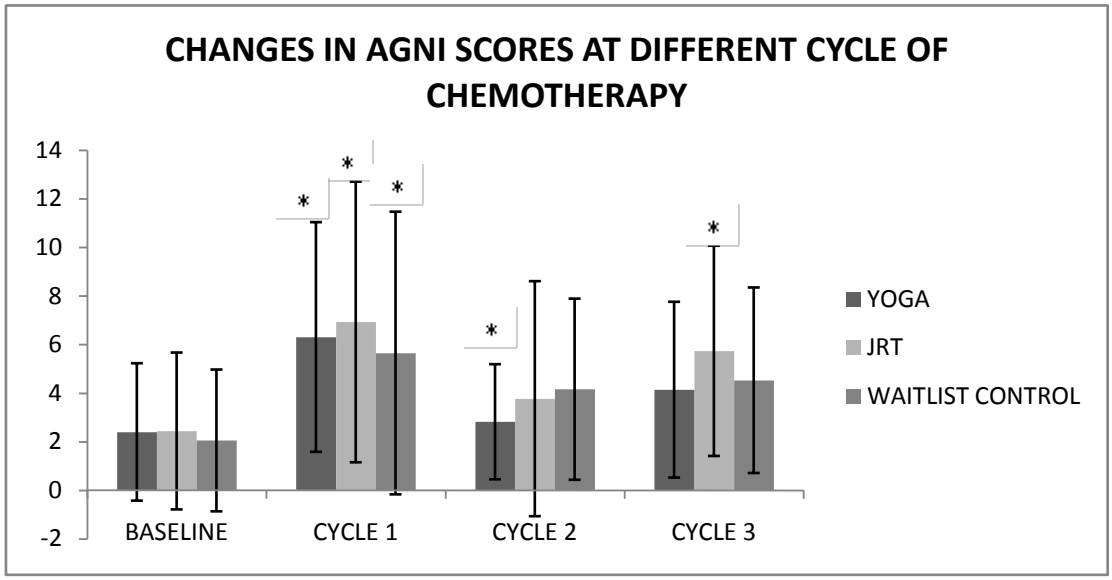
Within yoga group there was a significant increase in Agni impairment score between baseline and day 7 of first cycle (p<0.001) and decrease between Day 7 and second chemotherapy cycle (p=0.001). In Jacobson's group there was a significant increase between baseline and day 7 of first cycle (p=0.001) and 4th chemotherapy cycle (p=0.004). There was a significant increase in Agni scores between baseline and Day 7 of first cycle (p<0.001) in Control (Waitlist) group. Though there was a trend for decreases in Agni impairment scores in yoga group it was not significant between groups.

Table 6.5. Comparison of Agni scores between groups using repeated measures ANOVA

Chemotherapy	YOGA	JPMRT	CONTROL
	N=38	N=39	N=32
	Mean ± SD	Mean ± SD	Mean ± SD
C0	2.40 ±2.83	2.44 ±3.23	2.05±2.92
C1	6.31 ±4.73***	6.93± 5.78**	5.65±5.82**
C2	2.82±2.37**	3.77±4.84	4.16±3.73
C3	4.14 ±3.62	5.74±4.33**	4.53±3.82

p<0.01, ***p<0.001 for changes in Agni between baseline and subsequent chemotherapy cycles. **Conclusion: Decrease in Agni impairment in yoga group

Fig. 6.3:Changes in Agni scores at different cycle of chemotherapy



* Change in Agni between baseline and subsequent chemotherapy cycles.

6.2.1.3 Quantity of meal

Quantity of meal was assessed as an ordinal response variable. There was no significant change in quantity of meal between Yoga, Jacobsons and Control (Waitlist) group at baseline, day5-6 of 1st cycle and 2nd cycle of chemotherapy. There was a significant improvement in quantity of meal taken by end of 3rdcycle of chemotherapy in yoga group compared to Jacobsons group and controls indicating decrease in Agni impairment in yoga group (r=0.23, p=0.02).

Table 6.6.Comparison of quantity of meal taken at each chemotherapy cycle.

CYCLE	GROUP	**0 (NONE)**	**1 (MILD)**	**2 (MODERATE)**	**3 (SEVERE)**	**PEARSONS R, P VALUE**
		N (%)	**N (%)**	**N (%)**	**N (%)**	
CYCLE 1 (Day 1)	YOGA	30(75.0)	8(20.0)	2(5.0)	0(0.0)	(0.02), (0.86)
	JRT	26(66.7)	7(17.9)	4(10.3)	2(5.1)	
	WLC	30(81.1)	3(8.1)	3(8.1)	1(2.7)	
CYCLE 1-D5/D7	YOGA	12(30.8)	14(35.9)	10(25.6)	3(7.7)	(0.10), (0.27)
	JRT	13(31.7)	15(36.6)	9(22.0)	4(9.8)	
	WLC	10(32.3)	8(25.8)	4(12.9)	9(29.0)	
CYCLE 2	YOGA	19(50.0)	12(31.6)	5(13.2)	2(5.3)	(0.06), (0.57)
	JRT	19(48.7)	15(38.5)	4(10.3)	1(2.6)	
	WLC	13(43.3)	9(30.0)	7(23.3)	1(3.3)	
CYCLE 3	YOGA	19(51.4)	14(37.8)	3(8.1)	1(2.7)	(0.23), (0.01)
	JRT	11(31.4)	15(42.9)	5(14.3)	4(11.4)	
	WLC	9(32.1)	9(32.1)	7(25.0)	3(10.7)	

Abbreviations: JRT-Jacobson's relaxation technique. WLC-Wait list control.

significant improvement in quantity of meal taken, by the end of 3rdcycle of chemotherapy in yoga group

6.2.2 Secondary outcome measures

There was a significant decrease in **acute and delayed nausea severity** in Yoga compared to control group (p=0.001) and Jacobson's group (p=0.004) after 1st cycle of chemotherapy.

There was a significant decrease in **self-reported anxiety and depression** in Yoga (p=0.03) and Jacobson's relaxation (p=0.004) compared to control group following 3rd cycle of chemotherapy.

There was significant decrease in **LF/HF ratio** of HRV in Yoga group compared to control group (p=0.06) after 3rd cycle of chemotherapy.

There was a significant **decrease in bradygastria (p=0.002) and tachygastria** percentage (p=0.03) in Yoga group compared to Jacobson's and control group becoming more evident after 3rd cycle of chemotherapy.

6.2.2.1 Functional living index of emesis (FLIE) scores:

FLIE questionnaire was assessed at baseline, 6th day following 1st cycle and 5th day following 2nd cycle and 3rd cycle of chemotherapy.

a) FLIE-Nausea domain

Repeated measures ANOVA was carried out to compare the 3 groups (Yoga , Jacobson's and Control (Waitlist) over 4 time points (baseline pre chemotherapy (T1), 6 days post 1st cycle (T2), 5 days post 2nd cycle (T3) and 3rd cycle of chemotherapy(T4) to evaluate for group - time interaction effects. Overall multivariate analysis was significant with $F(2,192) = 2.99$, $p=0.007$. The between subjects effects was significant with $F(2, 97) = 3.69$, $p= 0.03$. The post hoc tests using Bonferroni correction showed

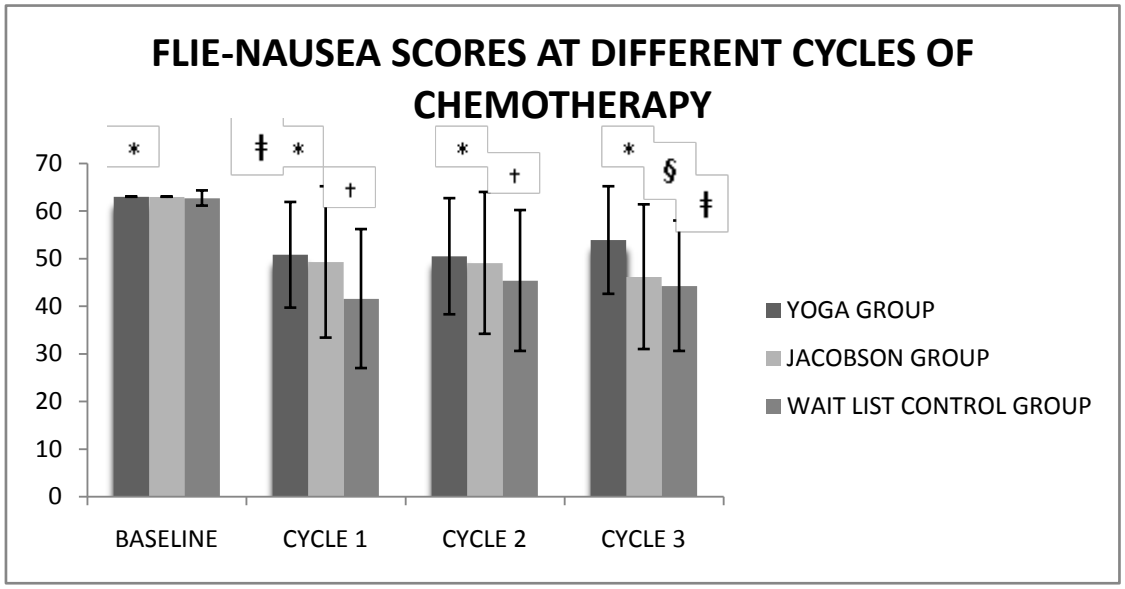
significant difference between T1 and T2 (p<0.001), T1 and T3 (p<0.001) and T1 and T4 (p<0.001) within Yoga, Jacobson's and control groups. There was a significant difference between Yoga and controls [(p=0.04, 95% CI= (0.94 to 17.5)] and Jacobson's and control [(p=0.04), (95% CI=0.30 to 16.9)] at 6th day following first cycle and Yoga vs Jacobson's relaxation [(p=0.05),(95% CI=0.03 to 15.2)] and Yoga vs controls [(p=0.02), (95% CI=1.2 to 17.8)] at 3rd cycle of chemotherapy using post hoc Bonferroni correction (See table 6.7).

Table 6.7: Comparison of pre-treatment functional living index–Nausea domain between Yoga, Jacobson's and Control (Waitlist) group using repeated measures ANOVA.

GROUP	n	C0	C1	C2	C3
		FLIE-N-T1	FLIE-N-T2	FLIE-N-T3	FLIE-N-T4
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Yoga	42	63 ± 0	50.8 ± 11.13***†	50.5 ± 12.2***	53.9 ± 11.3***†§
JPMRT	41	63 ± 0	49.3 ± 15.9*** ǂ	49.11 ± 14.9*** ǂ	46.2 ± 15.2***
Control	37	62.73 ± 1.6	41.69 ± 14.6***	45.4 ± 14.8***	44.39 ± 13.7***

*p<0.05, **p<0.01, ***p<0.001 for within group effects.†p<0.05 between Yoga vs. control, ǂ p<0.05 between Jacobson's vs. Control, § p<0.05 between Yoga vs. Jacobson's. FLIE-N: Functional living index emesis –Nausea domain.
Conclusion: There was a significant difference between Yoga vs Jacobson's relaxation and Yoga vs control group

Fig. 6.4: FLIE-Nausea scores at different cycles of chemotherapy



* within group effects; † between Yoga vs. control, ǂ between Jacobson's vs. Control. § between Yoga vs. Jacobson's.

Note: There was a significant difference between Yoga vs Jacobson's relaxation and Yoga vs control group

b) FLIE-Vomiting domain:

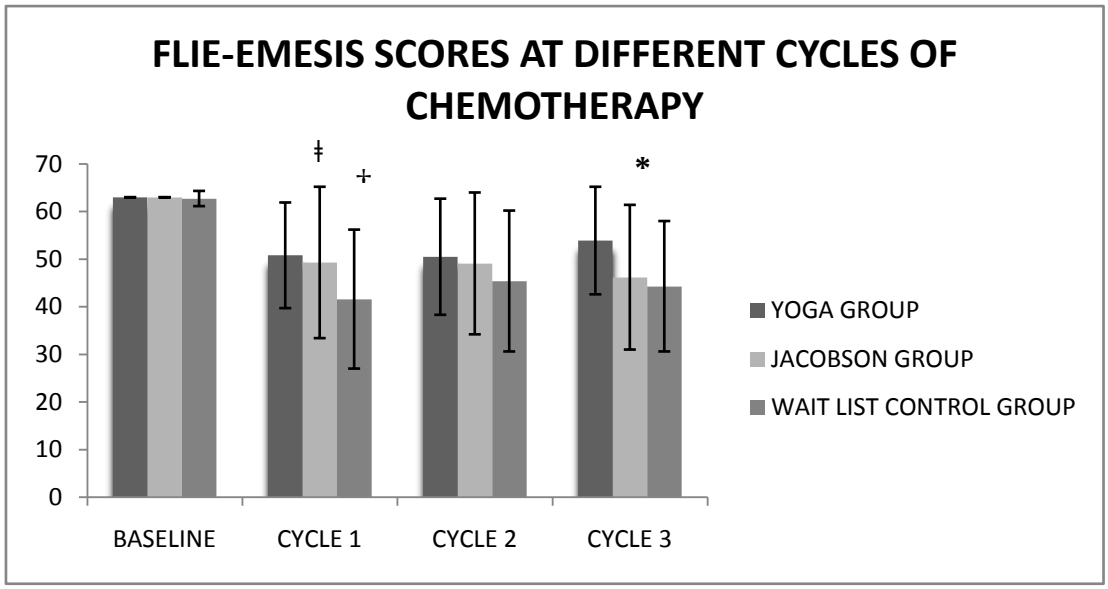
Repeated measures ANOVA was carried out to compare 3 groups (Yoga , Jacobson's and Control (Waitlist) over 4 time points (baseline pre chemotherapy (T1), 6 days post 1st cycle (T2), 5 days post 2nd cycle (T3) and 3rd cycle of chemotherapy (T4) to evaluate any group by time interaction effects. Overall multivariate analysis was significant with F (6,190) = 2.23 p=0.04. Post hoc tests using Bonferroni correction showed significant difference between T1 and T4 (p=0.05) in Yoga and Jacobson's group, T1 and T2 (p<0.001) and T1 and T3 (p=0.01), T2 and T3 (p<0.001 and T2 and T4 (p=0.003) in Control (Waitlist) group alone. There was a significant difference between Yoga and controls [(p=0.006, 95% CI= (1.8 to 14.1)] and Jacobson's and control [(p=0.007), (95% CI=1.8 to 14.2)] at 6th day following first cycle of chemotherapy using post hoc Bonferroni correction (See table 6.8).

Table 6.8: Comparison of functional living index–Emesis domain between Yoga, Jacobson's and Control (Waitlist) group using repeated measures ANOVA.

GROUP	n	C0	C1	C2	C3
		FLIE-VOM-T1	FLIE-VOM- T2	FLIE- VOM-T3	FLIE- VOM-T4
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Yoga	42	63.0 ± 0	59.03 ± 6.4††	60.11 ± 6.6	58.5 ± 9.4*
JPMRT	41	63.0 ± 0	57.9 ± 11.67‡‡	59.9 ± 7.9	58.4 ± 10.8*
Control	37	63.0 ± 0	50.5 ± 15.11***	57.3 ± 10.7**	58.4 ± 9.7**

*p<0.05, **p<0.01, ***p<0.001 for within group effects. †p<0.05 between Yoga vs. control, ‡ p<0.05 between Jacobson's vs. Control. FLIE-N: Functional living index emesis –Nausea domain.**Conclusion: Significant difference between Yoga vs control and Jacobson's vs control group.**

Fig. 6.5: FLIE-Emesis scores at different cycles of chemotherapy



* Within group effects, † between Yoga vs. control, ‡ between Jacobson's vs. Control.

Note: Significant difference between Yoga vs control and Jacobson's vs control group.

c) FLIE TOTAL: (Sum of both Nausea and Emesis)

A repeated measures ANOVA was carried out to compare 3 groups (Yoga , Jacobson's and Control (Waitlist) over 4 time points (baseline pre chemotherapy (T1), 6 days post 1st cycle (T2), 2nd cycle day 1(T3) and 3rd cycle day 1 of chemotherapy(T4)) to evaluate any group by time interaction effects. Overall multivariate analysis was significant with F (6,192) =2.96, p= 0.009. The between subjects effects was significant with F (2, 97) = 3.69, p= 0.03. However post hoc tests using Bonferroni correction showed significant difference between T1 and T2 (p<0.001), T1 and T3 (p<0.001) and T1 and T4 (p<0.001) within Yoga, Jacobson's and control groups . There was also a significant difference between T2 and T3 (p=0.009) and T2 and T4 (p=0.02) in Control (Waitlist) group. There was a significant difference between Yoga and controls [(p=0.004, 95% CI= (4.5 to 29.4)] and Jacobson's and control [(p=0.006), (95% CI=4 to 29.4)] at 6th day following first cycle of chemotherapy using post hoc Bonferroni correction (See table 6.9).

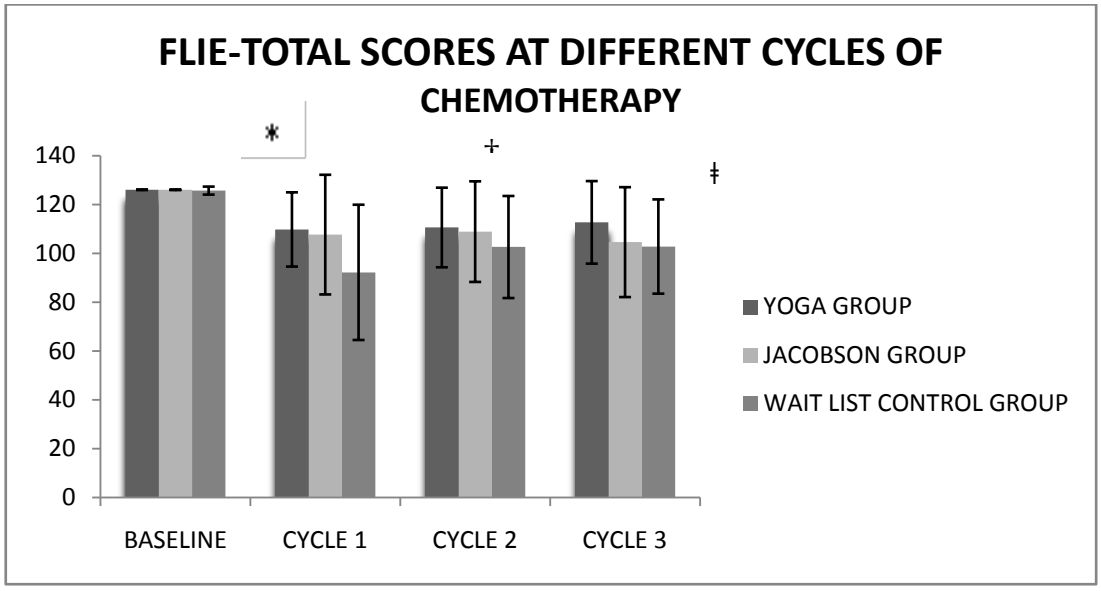
Table 6.9: Comparison of pre-treatment functional living index–Total between Yoga, Jacobson's and Control (Waitlist) group using repeated measures ANOVA.

GROUP	**CYCLE1 BASELINE**	**CYCLE1 DAY 6**	**CYCLE2 DAY 1**	**CYCLE3 DAY 1**
	FLIE TOTAL-T1	**FLIE TOTAL-T2**	**FLIE TOTAL-T3**	**FLIE TOTAL-T4**
Yoga Intervention Mean ± SD (N=42)	126.0 ± 0	109.79 ± 15.2*****††	110.6 ± 16.3***	112.7 ± 16.9***
Jacobson's relaxation Mean ± SD (N= 41)	126.0 ± 0	107.68 ± 24.5*** ǂǂ	108.9 ± 20.6***	104.6 ± 22.5***
Control (Waitlist) Mean ± SD (N=37)	125.7 ± 1.64	92.22 ± 27.7***	102.6 ± 20.9***	102.8 ± 19.3***

*p<0.05, **p<0.01, ***p<0.001 for within group effects. †p<0.05 between Yoga vs. control, ǂ p<0.05 between Jacobson's vs. Control ǂ p<0.001 between Jacobson's vs. Control. FLIE-N: Functional living index emesis –Nausea domain

Conclusion: Significant difference between Yoga vs control and Jacobson's vs control group

Fig. 6.6 :FLIE-total scores at different cycles of chemotherapy



* Within group effects. † Between Yoga vs. control, ǂ between Jacobson's vs. Control

ǂ $p<0.001$ between Jacobson's vs. Control

Note: Significant difference between Yoga vs control and Jacobson's vs control group

6.2.2.2 Nausea Diary:

Nausea diary was assessed every day for one week following every chemotherapy cycle for consecutive 3 cycles of chemotherapy. The average of all items on the questionnaire over a week was considered for analysis. Both acute and delayed nausea and emesis were assessed following each chemotherapy cycle. Acute emesis/nausea was considered as having nausea or emesis in first 24 hrs of chemotherapy administration. Anything above that was construed as delayed nausea and emesis.

a) Acute Nausea and Emesis:

Acute nausea percentage: was obtained from values on a visual analogue scale for 1st 24 hrs following chemotherapy for all 3 cycles. A repeated measures ANOVA was carried out to compare 3 groups (Yoga , Jacobson's and Control (Waitlist) over 3 time points (T1- day 1 following 1st cycle of chemotherapy, T2- day 1 following 2nd cycle of chemotherapy and T3 - day 1 following 3rd cycle of chemotherapy to evaluate any

group by time interaction effects. Overall multivariate analysis was not significant with F (4, 192) = 0.55 and between subjects effects was also not significant with F (4, 96) = 0.96. Post hoc tests using Bonferroni correction within and between groups did not show any significance.

Acute nausea severity: was assessed for 1st 24 hrs following chemotherapy for all 3 cycles. A repeated measures ANOVA was carried out to compare 3 groups (Yoga , Jacobson's and Control (Waitlist) over 3 time points (T1- day 1 following 1st cycle of chemotherapy, T2- day 1 following 2nd cycle of chemotherapy and T3 - day 1 following 3rd cycle of chemotherapy) to evaluate any group by time interaction effects. Overall multivariate analysis was not significant with F (2, 192) = 0.39 and between subjects effects was also not significant with F (2, 96) = 0.93. Post hoc tests using Bonferroni correction between groups did not show any significant changes. However there was significant decrease in nausea severity in Yoga group only between T1 and T3 (p=0.005).

Acute emesis severity: was assessed for 1st 24 hrs following chemotherapy for all 3 cycles. Repeated measures ANOVA was carried out to compare 3 groups (Yoga , Jacobson's and Control (Waitlist) over 3 time points (T1- day 1 following 1st cycle of chemotherapy, T2- day 1 following 2nd cycle of chemotherapy and T3 - day 1 following 3rd cycle of chemotherapy to evaluate any group by time interaction effects. Overall multivariate analysis was not significant with F (4, 192) = 0.37 and between subjects effects was also not significant with F (2, 96) = 1.72, p=0.18. Post hoc tests using Bonferroni correction within and between groups did not show any significant changes (See table 6.10).

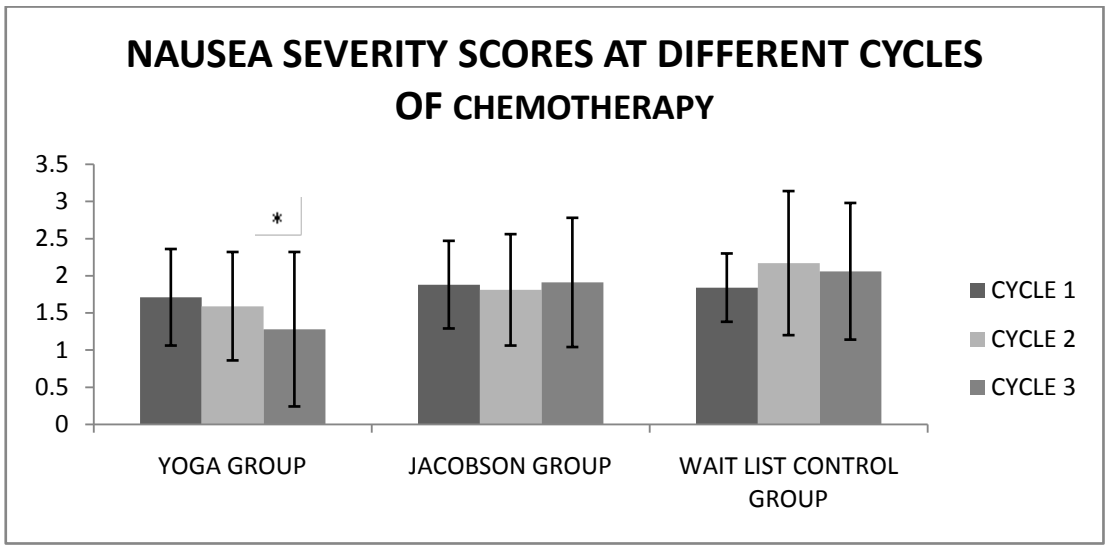
Table 6.10: Comparison of acute Nausea, Emesis percentage and severity of Nausea and Emesis between Yoga, Jacobson's and Control (Waitlist) group using repeated measures ANOVA

	NAUSEA %			NAUSEA SEVERITY			EMESIS SEVERITY		
GROUP	**C1**	**C2**	**C3**	**C1**	**C2**	**C3**	**C1**	**C2**	**C3**
Yoga Intervention Mean ± SD (N=42)	13.6 ± 14.7	14.41 ± 14.52	7.63 ± 12.4	1.71 ± 0.65	1.59 ± 0.59	1.28 ± 0.46**	0.22 ± 0.36	0.13 ± 0.28	0.11 ± 0.23
Jacobson's relaxation Mean ± SD (N= 41)	14.94 ± 17.6	13.88 ± 19.4	17.12 ± 27.8	1.88 ± 0.73	1.81 ± 0.75	1.91 ± 0.97	0.08 ± 0.15	0.05 ± 0.14	0.06 ± 0.19
Control (Waitlist) Mean ± SD (N=32)	17.84 ± 24.4	19.86 ± 22.4	24.32 ± 23.6	1.84 ± 1.04	2.17 ± 0.87	2.06 ± 0.92	0.18 ± 0.32	0.15 ± 0.27	0.18 ± 0.29

*p<0.05, **p<0.01, ***p<0.001 for within group effects

Conclusion: Significant decrease in nausea severity in Yoga group only

Fig. 6.7: Nausea severity scores at different cycles of chemotherapy



* Within group effects. Note: Significant decrease in nausea severity in Yoga group only

Delayed nausea percentage: Nausea persisting for more 24hrs following chemotherapy is called delayed nausea. A repeated measures ANOVA was carried out to compare 3 groups (Yoga , Jacobson's and Control (Waitlist) over 3 time points (T1- day 7 following 1st cycle of chemotherapy, T2- day 7 following 2nd cycle of chemotherapy and T3 - day 7 following 3rd cycle of chemotherapy to evaluate any group by time interaction effects. Overall multivariate analysis was not significant with F (4, 196) = 1.56, p=0.18, but between subjects effects was significant with F (2, 98) = 3.10, p=0.05. Post hoc tests using Bonferroni correction within groups did not show any significant changes. However there was a significant decrease in percentage of delayed nausea post 3rd cycle of chemotherapy in Yoga group as compared to controls [(p=0.009), (95%CI= -30 to -3.3)].

Delayed nausea severity: A repeated measures ANOVA was carried out to compare 3 groups (Yoga , Jacobson's and Control (Waitlist) over 3 time points (T1- day 7 following 1st cycle of chemotherapy, T2- day 7 following 2nd cycle of chemotherapy and T3 - day 7 following 3rd cycle of chemotherapy to evaluate any group by time interaction effects. Overall multivariate analysis was significant with F (4, 198) =3.47, p=0.009 and between subjects effects was significant with F (2, 99) = 6.1, p=0.003. Post hoc tests using Bonferroni correction within groups showed significant decrease in severity of delayed nausea at 3rd cycle compared to 1st cycle (p=0.03)in Yoga group only. There was a significant decrease in nausea at 2nd cycle between Yoga vs. Control (Waitlist) [(p=0.002), (95% CI= -1.06 to -0.19)]and at 3rd cycle between Yoga vs Control (Waitlist) [(p=0.001),(95% CI= -1.3 to -0.29)] and Yoga vs Jacobson's relaxation [(p=0.004) ,(95% CI= -1.09 to -0.16)].

Delayed emesis: A repeated measures ANOVA was carried out to compare 3 groups (Yoga , Jacobson's and Control (Waitlist) over 3 time points (T1- day 7 following 1st cycle of chemotherapy, T2- day 7 following 2nd cycle of chemotherapy and T3 - day 7

following 3rd cycle of chemotherapy to evaluate any group by time interaction effects. Overall multivariate analysis was significant with F (4, 198) =3.38, p=00.01 and between subjects effects was significant with F (2, 99) = 4.89, p=0.009. Post hoc tests using Bonferroni correction within groups was not significant. However, there was a significant decrease in delayed emesis severity at 2nd cycle between Yoga vs. Control (Waitlist) [(p=0.01), (95% CI= -0.95 to -0.09)] and Jacobson's vs. Control (Waitlist) [(p=0.04), 95% CI= -0.89 to -0.02)] and at 3rd cycle between Yoga vs. Control (Waitlist)s[(p=0.001),(95% CI= -1.23 to -0.28)] and Yoga vs. Jacobson's relaxation [(p=0.04), (95% CI= -0.93 to -0.01)](See table 6.11).

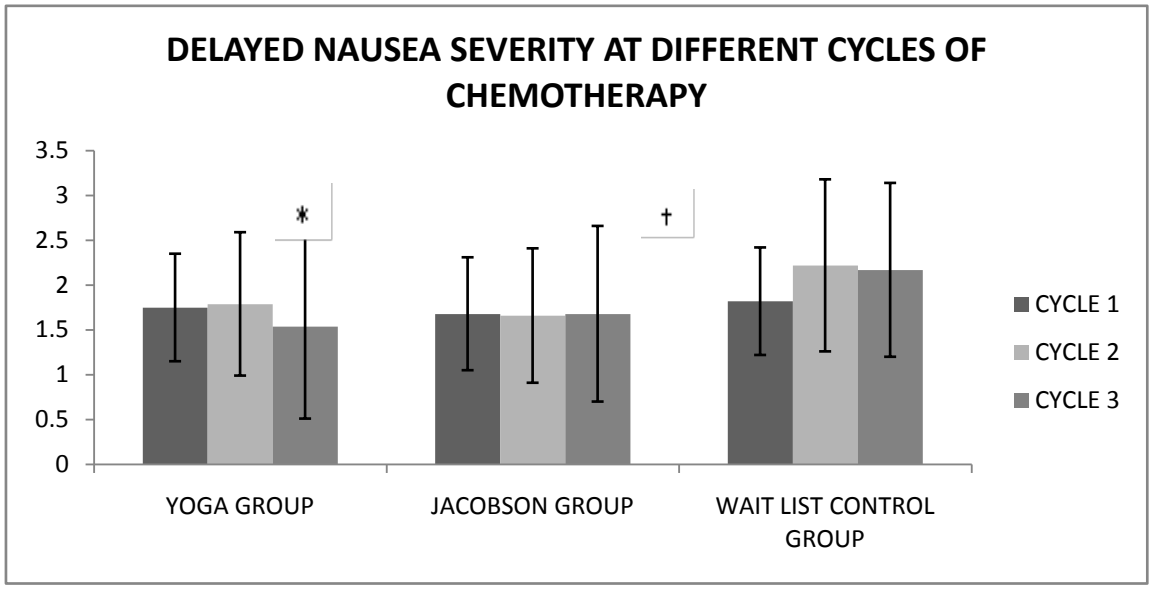
Table 6.11: Comparison of delayed Nausea, Emesis percentage and severity of Nausea and Emesis between Yoga, Jacobson's and Control (Waitlist) group using repeated measures ANOVA

GROUP	Delayed Nausea Percentage			Delayed Nausea Severity			Delayed Emesis Severity		
	T1	T2	T3	T1	T2	T3	T1	T2	T3
Yoga Intervention (N=41) Mean ±SD	15.37 ± 14.5	17.23** ± 16.1	20.0 ± 23.6	1.75 ± 23.6	1.79 ± 0.63	1.54**† ± 0.60	0.22 ± 0.36	0.13 ± 0.28	0.11 ± 0.23
Jacobson's relaxation (N=41) Mean ±SD	13.82 ± 18.1	13.88 ± 19.4	17.1 ± 27.7	1.68 ± 0.80	1.66 ± 0.75	1.68 ± 0.96	0.08 ± 0.15	0.05 ± 0.14	0.06 ± 0.19
Control (Waitlist) Mean ±SD (N=33)	17.19 ± 24.5	16.98 ± 23.7	18.86 ± 25.4	1.82 ± 1.03	2.22 ± 0.98	2.17 ± 0.97	0.19 ± 0.32	0.15 ± 0.27	0.18 ± 0.29

*p<0.05, **p<0.01, ***p<0.001 for within group effects. †p<0.05 between Yoga vs. control, ǂ p<0.05 between Jacobson's vs. Control, § p<0.05 between Yoga vs. Jacobson's.

Conclusion: Significant decrease in severity of delayed nausea within Yoga group and between Yoga vs. Control (Waitlist) group

Fig. 6.8: Delayed nausea severity at different cycles of chemotherapy



* within group effects † between yoga vs. control, ǂ between Jacobsons vs. Control, § between yoga vs. Jacobson's.

Note:Significant decrease in severity of delayed nausea within Yoga group and between Yoga vs. Control (Waitlist) group.

6.2.2.3 Psychological outcomes:

a) Hospital anxiety and depression Score – Anxiety

There was a significant decrease in anxiety on HADS in Yoga [(t =2.19, p = 0.03), (95% CI= 0.22 to 4.4)] and Jacobson's groups [(t =3.02, p = 0.004), (95% CI= 1.2 to 5.7)] compared to Control (Waitlist) group. There was a significant decrease in anxiety scores within Yoga (t =3.96, p < 0.001) and Jacobson's group (t = 4.76, p< 0.001) following intervention (See Table 6.12).

b) Hospital anxiety and depression Score – Depression

There was a significant decrease in depression on HADS in Yoga [(t=1.93, p=0.05), (95%CI= -0.04 to 4.4)] and Jacobson's groups [(t=3.6, p=0.001), (95%CI= 1.7 to 6.2)] compared to Control (Waitlist) group. There was a significant increase in depression scores in Control (Waitlist)s at 4th chemotherapy cycle compared to baseline (t=-3.69, p=0.001) on paired t test (See Table 6.12).

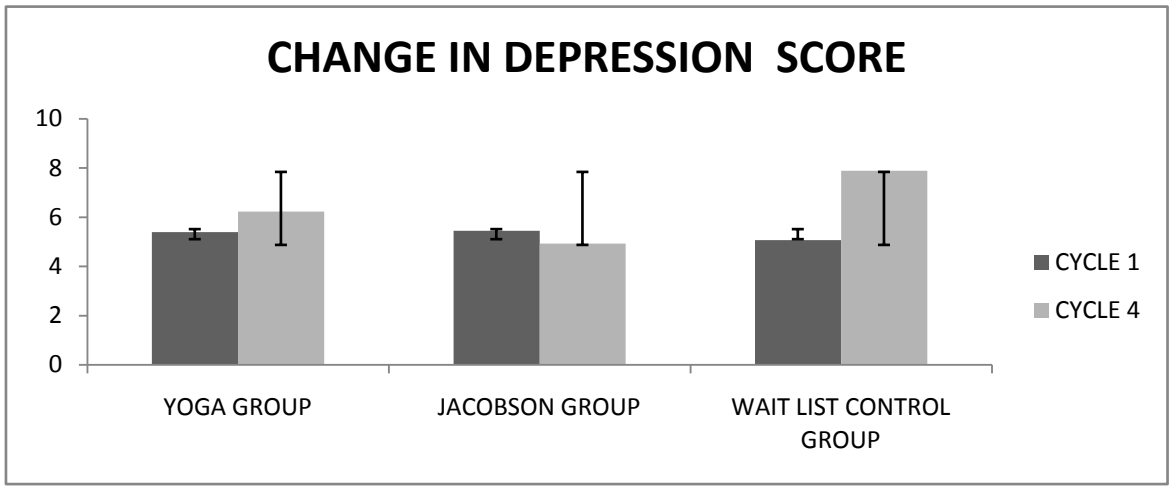
Table 6.12: Comparison of anxiety and depression scores between Yoga, Jacobson's and Control (Waitlist) group using Independent samples t test.

GROUP	HADS- ANXIETY			HADS- DEPRESSION		
	T1	T4	Change	T1	T4	Change
Yoga Intervention (N=42) Mean ± SD	8.52 ± 4.9	5.14***§ ± 3.6	2.78 ± 4.3	5.40 ± 4.1	5.65§ ± 4.2	-0.70 ± 4.8
Jacobson's relaxation (N=41) Mean ± SD	8.71 ± 4.7	5.33***ǂ ± 3.5	3.92 ± 4.9	5.46 ± 4.1	4.94 ǂ ± 3.3	1.03 ± 4.5
Control (Waitlist) (N=37) Mean ± SD	8.05 ± 4.5	7.63 ± 4.8	0.43 ± 4.4	5.08 ± 4.2	7.90 ± 4.6	-2.90 ± 4.3

p<0.05, **p<0.01, ***p<0.001 for within group effects. †p<0.05, ††p<0.001 between Yoga vs. control, ǂ p<0.05 between Jacobson's vs. Control.

Conclusion: Significant decrease in anxiety scores within Yoga and Jacobson's group. Significant decrease in depression within Yoga and Jacobson's group.

Fig. 6.9: Change in depression score



§ Between Yoga vs. Jacobson's between Jacobson's vs. Control, § p<0.05 between Yoga vs. Jacobson's.

Note: Significant decrease in depression within Yoga and Jacobson's group.

c) Spielberger's state Trait Anxiety Inventory –State Anxiety

STAI-state Anxiety was assessed at baseline at 6th day 1st cycle, at 2nd cycle and after 3rd cycle of chemotherapy**.** repeated measures ANOVA was carried out to compare 3 groups (Yoga , Jacobson's and Control (Waitlist)s) over 4 time points (baseline pre chemotherapy (T1), 6 days post 1st cycle (T2), 2nd cycle day 1(T3) and after 3rd cycle of chemotherapy(T4)) to evaluate any group by time interaction effects. Overall multivariate analysis was not significant with F (6,188) =0.833,p= 0.55. The between subjects effects was significant with F (2, 95) = 3.51, p= 0.03. However post hoc tests using Bonferroni correction did not show any significant difference within groups. There was a significant difference between Yoga and controls [(p=0.03, 95% CI= (-15.5 to-0.51)] and Jacobson's and control [(p=0.03), (95% CI= -15.6 to -0.65)] following 3rd cycle of chemotherapy using post hoc Bonferroni correction (See Table 6.13).

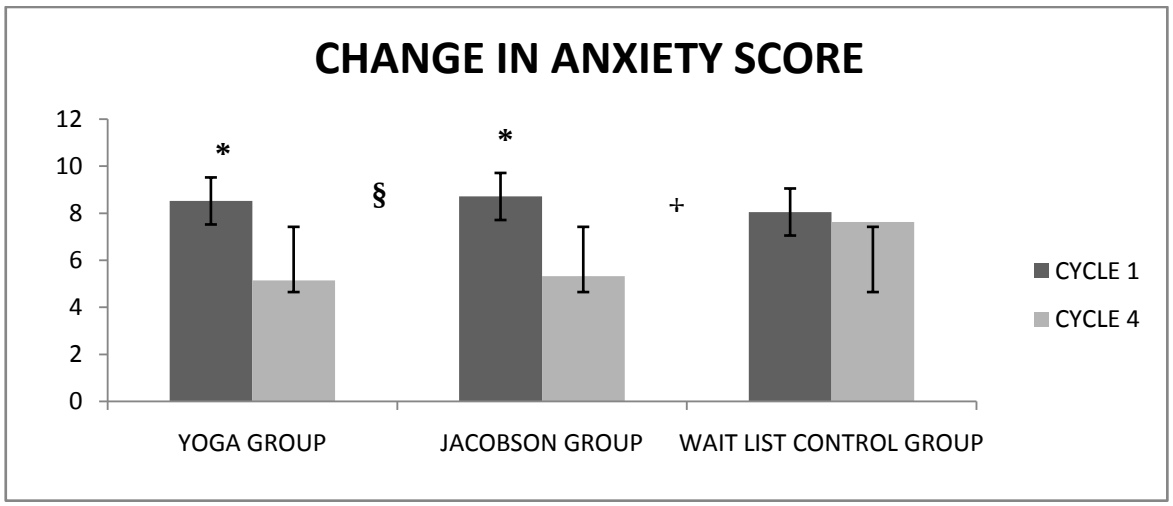
Table 6.13: Comparison of Stateanxiety inventory scores between Yoga, Jacobson's and Control (Waitlist) group using Independent samples t test.

GROUP	STAI	STAI	STAI	STAI
	T1	T2	T3	T4
Yoga Intervention(N=42) Mean ± SD	44.12± 14.7	41.1± 12.8	37.65± 10.3	36.5± 11.8
Jacobson's relaxation(N=42) Mean ± SD	43.15± 13.2	40.3± 13.6	36.95± 11.7	37.11± 10.4
Control (Waitlist)(N=36) Mean ± SD	44.92± 14.2	46.2± 12.1	44.24± 12.8	44.63± 14.1

†p<0.05 between Yoga vs. control, ǂ p<0.05 between Jacobson's vs. Control, § p<0.05 between Yoga vs. Jacobson's.

Conclusion: Significant difference between Yoga vs controls and Jacobson's vs control following chemotherapy in State anxiety inventory.

Fig. 6.10: Change in anxiety scorein State anxiety inventory



§ between Yoga vs. Jacobson's. * within group effects ǂ between Jacobson's vs. Control

Note:Significant difference between Yoga vs controls and Jacobson's vs control following chemotherapyin State anxiety inventory.

d) Perceived stress scores

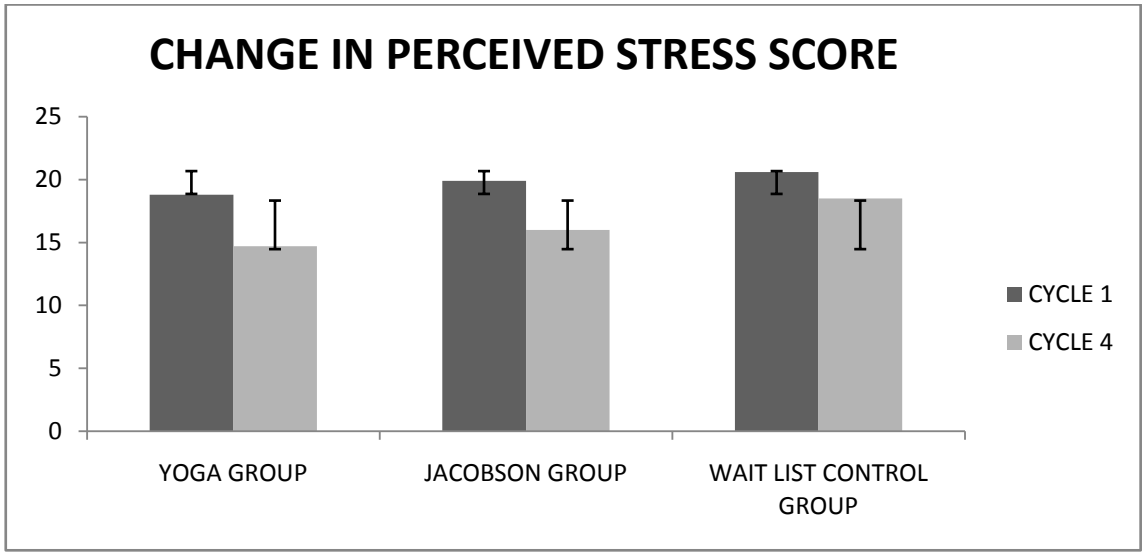
There was no significant difference between groups on perceived stress scores on independent samples t test. However there was a significant decrease in perceived stress in Yoga [t=2.82, p=0.008] and Jacobson's [t=4.99, p<0.001] group following intervention on paired t test (See Table 6.14).

Table 6.14: Comparison of Perceived stress scale scores between Yoga, Jacobson's and Control (Waitlist) group using Independent samples t test.

GROUP	T1 PSS	T4 PSS	CHN PSS
Yoga Intervention Mean ± SD(N=42)	18.83 ± 7.7	14.70 ± 6.4**	3.92 ± 8.5
Jacobson's relaxation Mean ± SD(N=41)	19.98 ± 5.6	16.03 ± 5.6***	4.64 ± 5.6

Control (Waitlist) Mean ± SD(N=37)	20.68 ± 11.1	18.57 ± 7.03	2.03 ± 10.8
*p<0.05, **p<0.01, ***p<0.001 for within group effects on paired t test. **Conclusion: Significant decrease in perceived stress within Yoga and Jacobson's group.**			

Fig. 6.11: Change in perceived stress score



* within group effects.

Note: Significant decrease in perceived stress in Yoga group

e) Cancer Locus of control scale

There was no significant difference between groups on cancer locus of control scale nor was there any significant change within groups following intervention (See Table 6.15).

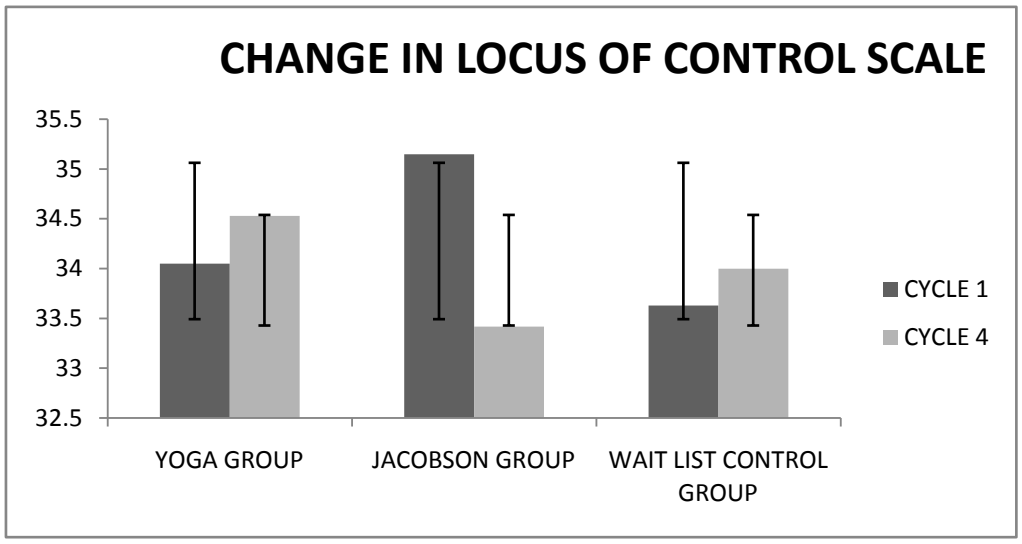
f) Profile of mood states

There was a significant increase in profile of mood states in Jacobson's group compared to Control (Waitlist) group following intervention [(t=2.11, *p*=0.04), (95%CI= 0.19 to7.8)]. There was a significant increase in profile of mood state score in Jacobson's group only (t=2.1, *p*=0.04) following intervention (See Table 6.15).

Table 6.15: Comparison of Locus of control score between Yoga, Jacobson's and Control (Waitlist) group using Independent samples t test.

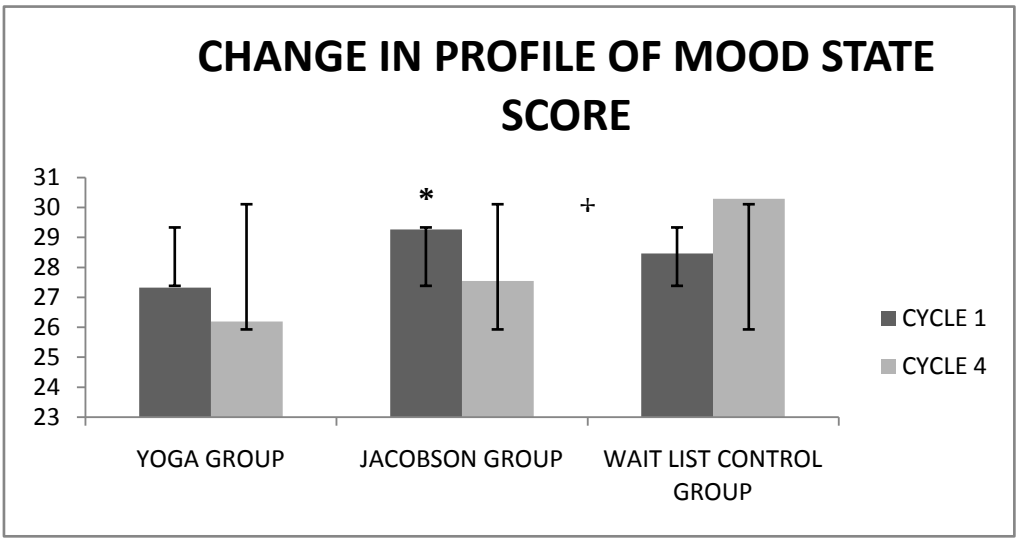
	LOCUS OF CONTROL			PROFILE OF MOOD STATE		
GROUP	**BASELINE**	**POST**	**CHANGE**	**BASELINE**	**POST**	**CHANGE**
Yoga Intervention Mean ±SD (N=39)	34.05 ± 6.6	34.53 ± 7.4	-0.12 ± 7.4	27.33 ± 7.7	26.20 ± 9.8	0.69 ± 8.5
Jacobson's relaxation Mean ±SD (N=40)	35.15 ± 6.5	33.42 ± 7.2	2.31 ± 7.7	29.27ǂ* ± 6.5	27.55 ± 7.2	2.50 ± 6.7
Control (Waitlist) Mean ±SD (N=35)	33.63 ± 7.2	34.0 ± 5.70	1.16 ± 7.6	28.47 ± 6.8	30.30 ± 8	-1.50 ± 7.5
*p<0.05 for within group effects, ǂ p<0.05 between Jacobson's vs. Control **Conclusion: Significant increase in profile of mood state score in Jacobson's group only**						

Fig. 6.12 : Change in locus of control scale



NO CHANGE

Fig. 6.13 :Change in profile of mood state score



* Within group effects, ǂ between Jacobson's vs. ControlNote: Significant increase in profile of mood state score in Jacobson's group

Electrogastrogram:

Each session was divided into two segments 20-min segments (fasting and water load stimulation) and computerized spectral analysis was performed on the data. The signal from the EGG was described by several quantitative parameters, including, percentage of normal 2–4 cpm, Bradygastria and Tachygastria slow waves. The observed parameters from the EGG signal were as follows.

Normal Slow waves %: *(2-3 cpm)*

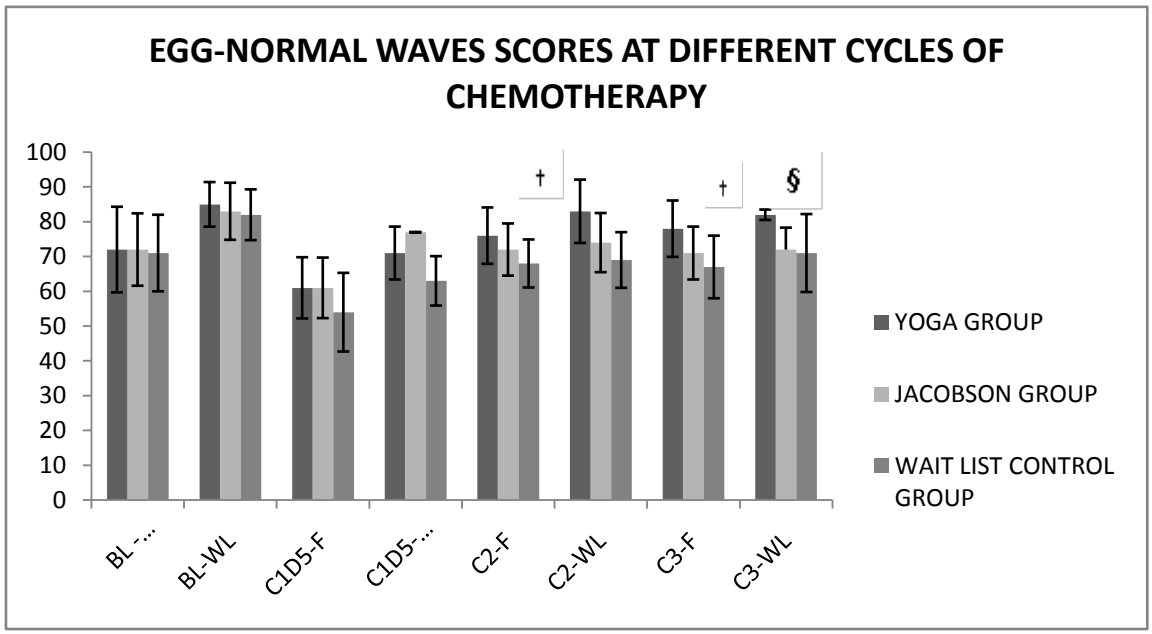
There was a significant increase in normal waves in yoga group compared to control group (t= 2.19, p=0.02) and Jacobson's group (t= 1.92,p=0.04) after 3rd cycle of chemotherapy. There was a significant increase in normal waves percent at 6th day following 1st cycle of chemotherapy in jacobsons group compared to control group (t= 2.12, p=0.04).

Table 6.16: Comparison of changes in gastric motility on surface EGG between Yoga, Jacobson's and Control group -Independent samples t test-<u>normal waves</u>

Normal waves (2-3 cpm)	Baseline Fasting (%)	Baseline Water load (%)	6th day 1st cycle fasting	6th day 1st cycle water load	2nd cycle fasting	2nd cycle water load	3rd cycle fasting	3rd cycle water load
Yoga group Mean±SD	72 ± 12.3	85 ± 6.4	61± 8.8	71 ± 7.6	76± 8.1	83± 9.11†	78± 8.1†	82± 1.5†
Jacobsons relaxation group Mean±SD	72 ± 10.4	83± 8.2	61± 8.7	77± 7.4ǂ	72± 7.5	74± 8.5	71± 7.6	72± 6.3§
Control group Mean±SD	71± 11	82± 7.3	54± 11.3	63± 7.1	68± 6.9	69± 8	67± 9	71± 11.2

*p<0.05, **p<0.01, ***p<0.001 for within group effects †p<0.05, ††p<0.01 between yoga vs. control, ǂp<0.05, ǂǂ p<0.01 between Jacobson's vs. Control, § p<0.05 between yoga vs. Jacobson's group. **Significant increase in normal waves in yoga group.**

Fig. 6.14:EGG-normal waves scores at different cycles of chemotherapy



* within group effects † between yoga vs. control, ǂ between Jacobsons vs. Control, § between yoga vs. Jacobsons

Bradygastria%:*(0.5 to 2 cpm)*

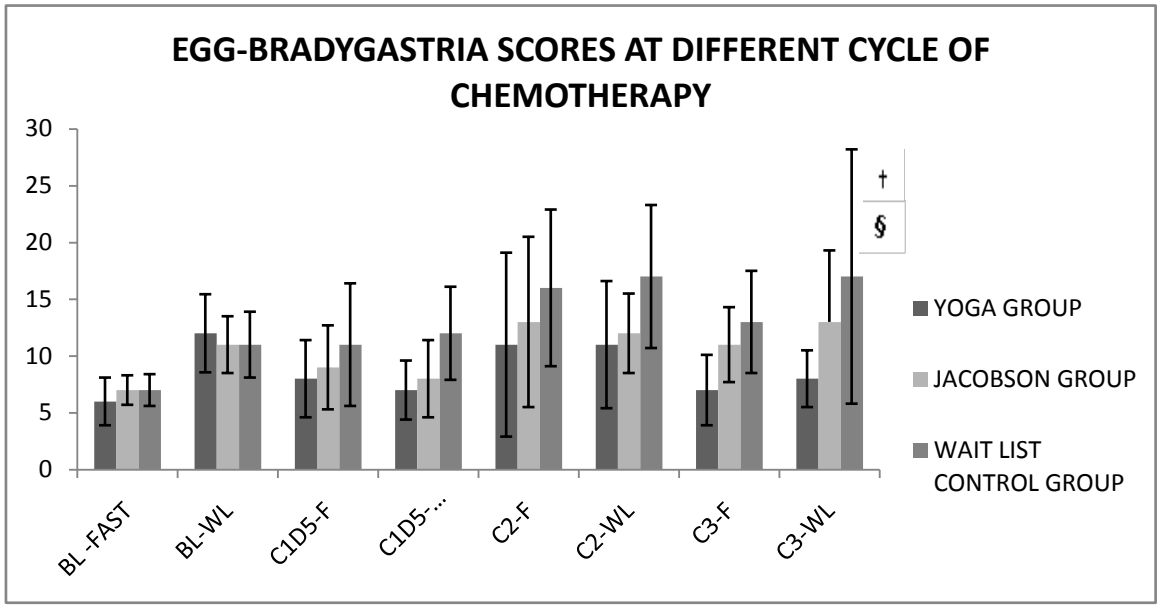
There was a significant decrease in bradygastriapercent in yoga group compared to control group (t= 2.39, p=0.01) at 6th day following 1st cycle of chemotherapy. There was a significant decrease in bradygastriapercent following 3rd cycle of chemotherapy in yoga group compared to control (t= 2.21, p=0.002) and in yoga group compared to jacobsonsgroup(t= 2.11, *p*=0.02).

Table 6.17: Comparison of changes in gastric motility on surface EGG between Yoga, Jacobson's and Control group -Independent samples t test-Bradygastria

Bradygastria % (0.5 to 2 cpm)	**Baseline Fasting (%)**	**Baseline Water load (%)**	**6th day 1st cycle fasting**	**6th day 1st cycle water load**	**2nd cycle fasting**	**2nd cycle water load**	**3rd cycle fasting**	**3rd cycle water load**
Yoga group Mean±SD	6 ± 2.1	12 ± 3.44	8 ± 3.4	7 ± 2.6††	11± 8.1	11± 5.6	7± 3.1	8± 2.5††
Jacobsons relaxation group Mean±SD	7 ± 1.3	11 ± 2.5	9 ± 3.7	8 ± 3.4	13 ± 7.5	12 ± 3.5	11 ± 3.3	13 ± 6.3§
Control group Mean±SD	7 ± 1.4	11 ± 2.9	11 ± 5.4	12 ± 4.1	16 ± 6.9	17 ± 6.3	13 ± 4.5	17 ± 11.2

*p<0.05, **p<0.01, ***p<0.001 for within group effects †p<0.05, ††p<0.01 between yoga vs. control, ǂp<0.05, ǂǂ p<0.01 between Jacobson's vs. Control, § p<0.05 between yoga vs. Jacobson's group. **Decrease in bradygastria in yoga group.**

Fig. 6.15 :EGG-Bradygastria scores at different cycle of chemotherapy



* Within group effects †between yoga vs. control, ǂ between Jacobsons vs. Control, § between yoga vs. jacobsons

Conclusion: Decrease in bradygastria in yoga group.

Tachygastriapercentage:*(3-5 cpm)*

There was a significant decrease in tachygastriapercent in resting EGG on 6th day of 1st cycle in jacobsons group compared to controls group (t= 3.21, p=0.002). There was a significant decrease in tachygastria percent in yoga group compared to control group (t= 2.3, p=0.03) after 3rd cycle of chemotherapy.

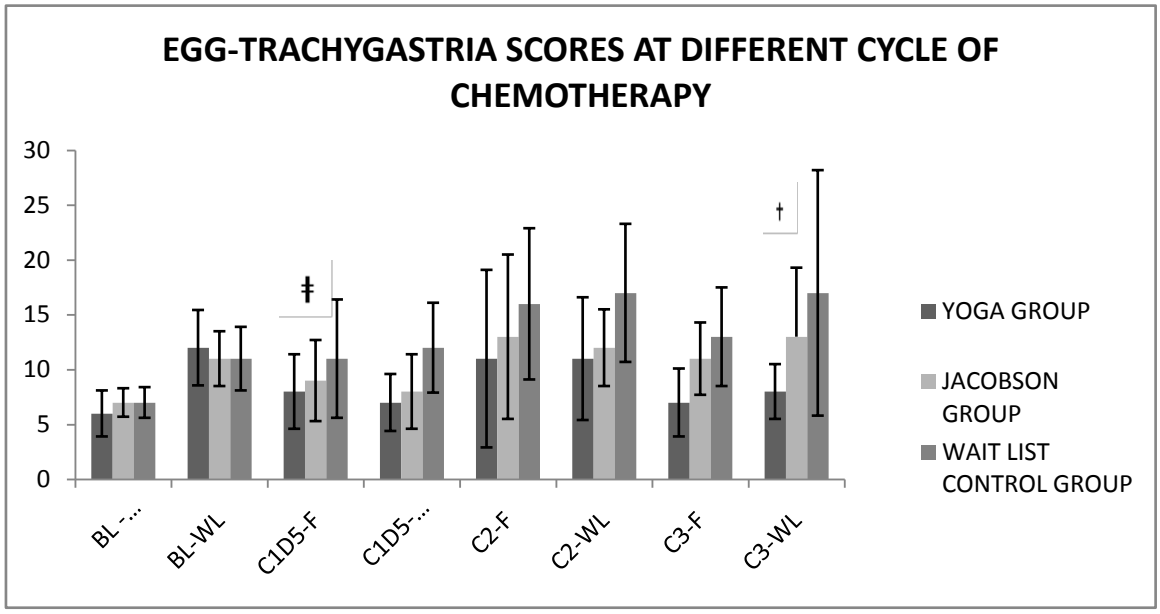
Table 6.18: Comparison of changes in gastric motility on surface EGG between Yoga, Jacobson's and Control group -Independent samples t test-Tachygastria

Tachygastria % (3-5 cpm)	**Baseline Fasting (%)**	**Baseline Water load (%)**	**6th day 1st cycle fasting**	**6th day 1st cycle water load**	**2nd cycle fasting**	**2nd cycle water load**	**3rd cycle fasting**	**3rd cycle water load**
Yoga group Mean ± SD	11.3 ± 2.67	12 ± 6.4	12 ± 3.4	12 ± 3.2	10 ± 4.2	11 ± 2.9	9 ± 2.8	10 ± 3.4†

Jacobson's relaxation group Mean±SD	10.4 ± 3.2	11 ± 6.2	10 ± 2.5 ǂ	12 ± 3.8	11 ± 3.8	12 ± 3.1	11 ± 3.5	12 ± 3.2
Control group Mean±SD	13.2 ± 3.3	14 ± 5.4	16 ± 3.8	15 ± 3.4	13 ± 4.5	14 ± 3.8	13 ± 3.8	16 ± 4.1

*p<0.05, **p<0.01, ***p<0.001 for within group effects †p<0.05, ††p<0.01 between yoga vs. control, ǂp<0.05, ǂ p<0.01 between Jacobson's vs. Control, § p<0.05 between yoga vs. Jacobson's group. **Significant decrease in tachygastria percent in Jacobson's group**

Fig. 6.16 : EGG-trachygastria scores at different cycle of chemotherapy



* Within group effects †between yoga vs. control, ǂ between Jacobson's vs. Control, § between yoga vs. Jacobson's.

Conclusion: Significant decrease in tachygastria percent in Jacobson's group

AUTONOMIC FUNCTION TEST:

The dependent variables were physiologic parameters, including both time and frequency domains. The time domain included heart rate and the 5- minute average R-R interval (SDANN). The frequency domain(for results refer Appendix)included total power, low-frequency (LF) power, high-frequency (HF) power, very-low-frequency (VLF) power, and LF/HF ratio Both the SDANN and total power values reflect the total ANS activity (Malik M,1996). LF power reflects sympathetic nervous system activity (Malik M,1996; Pagani M,1986) or the autonomic outflows for baroreflex modulation (Moak JP,2009) .In contrast, HF power reflects parasympathetic nervous system activity. The LF/ HF ratio represents the balance between sympathetic and parasympathetic activity (Malik M. 1996).

Both frequency and time domain analysis of HRV was carried out. The data were not normally distributed and we decided to analyze the data using Independent samples Mann Whitney Test and within groups Wilcoxon's sign rank test.

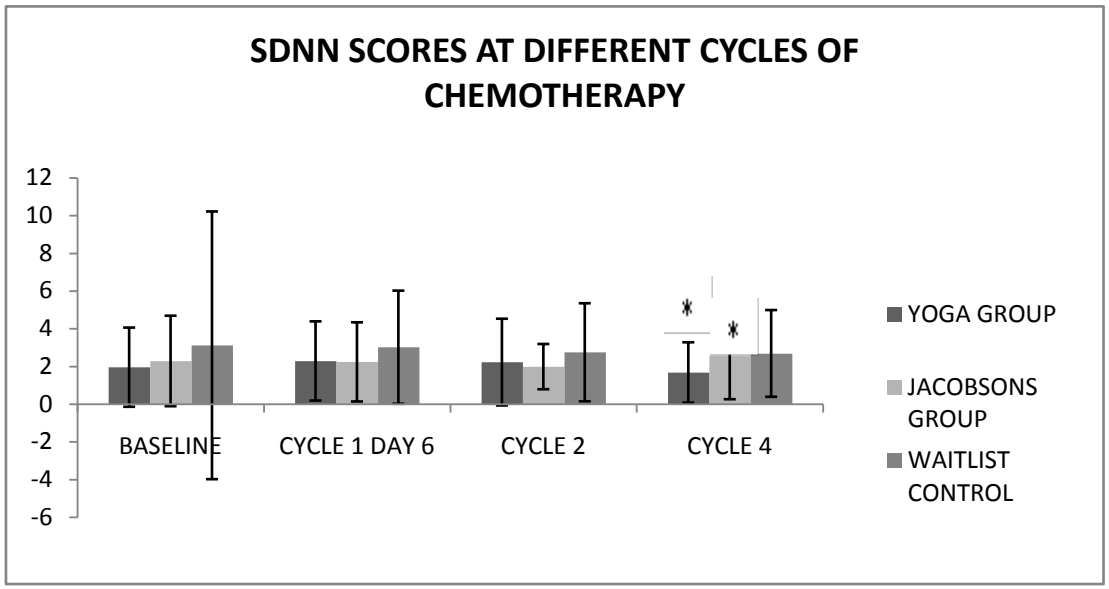
Standard deviation of NN interval: There was a significant decrease in SDNN after 3rd cycle of chemotherapy in yoga group (Z =-2.17, p=0.03) and Jacobson's group (Z =-2.17, p=0.03), compared to baseline on Wilcoxon's sign rank test. There was no significant difference between groups.

Table 6.19: Comparison of SDNN (Standard deviation of NN interval) between Yoga, Jacobson's and Control (Waitlist) group using Non parametric independent sample Mann-Whitney test.

GROUP	SDNN			
	BASELINE	CYCLE 1 DAY 6	CYCLE 2	CYCLE 4
Yoga group(N=39) Mean ± SD	27.22 ± 15.6	26.95 ± 19.7	31.99 ± 27.1	23.7 ± 14.2*

Jacobson's group(N=36) Mean ± SD	30.35 ± 14.6	24.54 ± 10.1	25.40 ± 11.6	22.76 ± 10.8*****
Control(N=30) Mean ± SD	29.99 ± 19.2	21.61 ± 12.1	22.61 ± 13.1	19.77 ± 13.6
*p<0.05, **p<0.01, ***p<0.001 for within group effects. **Conclusion: Significant decrease in yoga and Jacobson's group in SDNN**				

Fig. : 6.17: SDNN scores at different cycles of chemotherapy



* Within group effects

Conclusion: Significant decrease in SDNN after 3rd cycle of chemotherapy in yoga group and Jacobson's group

Delta NN: There was a significant increase in Delta NN after 3rd cycle of chemotherapy in yoga group compared to control group (z=-2.57, 0.01) on independent Mann Whitney test. There was a significant decrease in delta NN on Wilcoxons sign rank test in Jacobson's groups after 3rd cycle of chemotherapy (z=-2.03, p=0.04) and in control group at 2nd cycle (Z=-2.27, p=0.02) and after 3rd cycle of chemotherapy (Z=- 2.05, p=0.04).

Table 6.20: Comparison of DELTA NN between Yoga, Jacobson's and Control (Waitlist) group using Non parametric independent sample Mann-Whitney test.

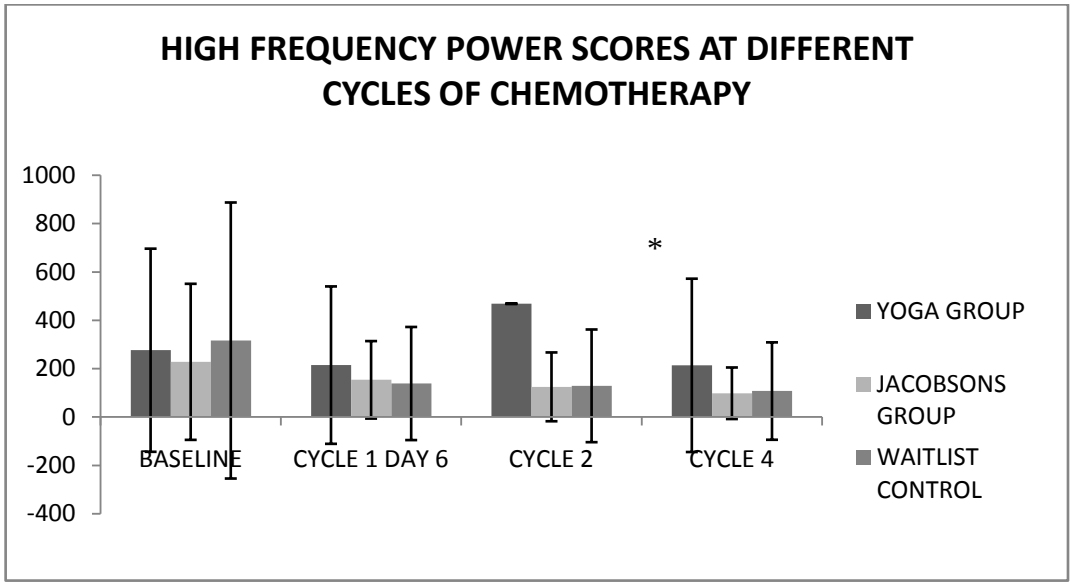
GROUP	DELTA NN			
	BASELINE	CYCLE 1 DAY 6	CYCLE 2	CYCLE 4
Yoga group Mean ± SD (N=39)	22.37 ± 18.6	20.96 ± 16.2	27.93 ± 30.7	18.67 ± 12.7**
Jacobson's group Mean ± SD (N=36)	21.86 ± 16.4	18.06 ± 10.2	16.63 ± 9	16.44 ± 14*
Control Mean ± SD (N=30)	27.64 ± 29.3	15.86 ± 13.5	14.32 ± 10.2*	12.11 ± 9.4*
*p<0.05, **p<0.01, ***p<0.001 for within group effects. **Conclusion**: **Significant increase in yoga group compared to decrease in Jacobson's group.**				

High frequency power: There was a significant increase in high frequency power in yoga group compared to control group after 3rd cycle of chemotherapy (Z=-2.28, p=0.02). There was significant decrease in high frequency power in control group (z=-2.38, p=0.02) after 3rd cycle of chemotherapy compared to baseline.

Table 6.21: Comparison of High frequency power between Yoga, Jacobson's and Control(Waitlist) group using Non parametric independent sample Mann-Whitney test.

GROUP	HFP (ms^2)			
	BASELINE	CYCLE 1 DAY 6	CYCLE 2	CYCLE 4
Yoga group(N=39) Mean ± SD	276.29 ± 420	214.71 ± 325.5	468.72 ± 1.3	213.75 ± 358.4*
Jacobson's group(N=36) Mean ± SD	228.32 ± 322.7	153.91 ± 160.2	124.87 ± 142.3	98.39 ± 106.6
Control group(N=30) Mean ± SD	316.50 ± 570.8	138.63 ± 233.9	129.07 ± 233	107.45 ± 201.4*
*p<0.05, **p<0.01, ***p<0.001 for within group effects **Conclusion: Significant increase in yoga group in high frequency power**				

Fig. : 6.18: High Frequency Power Scores at Different Cycles of Chemotherapy



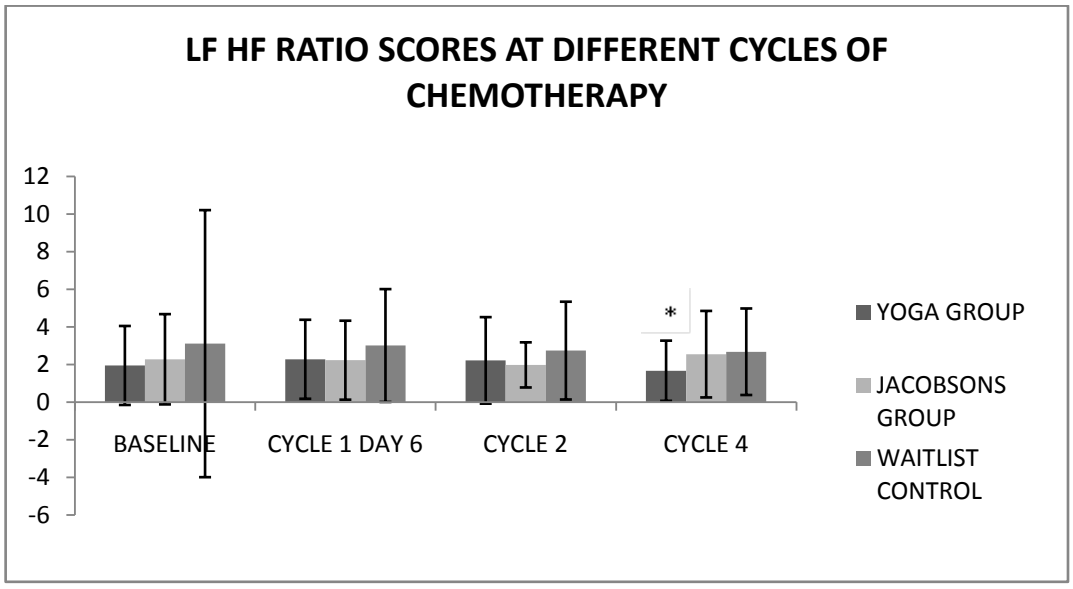
* Within group effects; Significant increase in yoga group in high frequency power

LF/HF RATIO: There was significant decrease in LF/HF ratio in yoga group compared to control group (Z=-1.8, p=0.06) after 3rd cycle of chemotherapy. There was a significant decrease in LF/HF ratio after 6days of 1st cycle of chemotherapy compared to baseline (z=-2.06, p=0.03) in Jacobson's group.

Table 6.22: Comparison of Low frequency and high frequency ratio between Yoga, Jacobson's and Control (Waitlist) group using Non parametric independent sample Mann-Whitney test.

GROUP	LF/ HF RATIO			
	BASELINE	CYCLE 1 DAY 6	CYCLE 2	CYCLE 4
Yoga group(N=39) Mean ± SD	1.95 ± 2.1	2.28 ± 2.1	2.22 ± 2.3	1.67 ± 1.6**
Jacobson's group(N=36) Mean ± SD	2.28 ± 2.4	2.23 ± 2.1	1.98 ±1.2	2.55 ± 2.3*
Control group(N=30) Mean ± SD	3.11 ± 7.1	3.01 ± 3	2.74 ± 2.6	2.68 ± 2.3
*p<0.05, **p<0.01, ***p<0.001 for within group effects **Conclusion: Significant decrease in yoga group in LF/HF ratio**				

Fig. : 6.19: LF:HF Ratio Scores at Different Cycles of Chemotherapy



* Within group effects

Significant decrease in LF/HF ratio in yoga group compared to control group after 3rd cycle of chemotherapy.

Chapter 7

DISCUSSION

In the present study a holistic approach was used to capture the cluster of symptoms for managing the chemotherapy induced nausea and emesis as these symptom clusters have not been given their due importance due to subtle and subjective nature of their presentation. Āyurveda texts describe concept of Jāṭharāgni, a form of Agni impairment that manifests as symptom clusters. As per ancient texts Jāṭharāgni is a physiological entity which converts the substance from biological level to physiological level. It is subtle and its presence can only be felt and observed but not seen. According to Āyurveda texts this Jāṭharāgni is the physiological principle that governs all GI functions including digestion, assimilation and excretion through a regulated release of digestive juices and enzymes and timed gastric motility and any impairment will lead to exacerbation of these GI symptoms (śabdakalpadrum) (Haridāsa saṁskrutha granthamāla 106 Chap 11 Verse 34, Chap3Verse 50-54), (Trikamji, 1935 Chap 15 Verse 3). In this study a comprehensive checklist was developed and standardised to capture and measure these symptoms as a measure of Jāṭharāgni impairment. Results suggested that there was strong reliability for JIC to measure impairment in Agni. There was a poor agreement between FLIE and Agni scores indicating strong discriminate validity and suggesting that JIC measures a construct different from that of FLIE (measures only Nausea and Vomiting). But at the same time JIC measures the impact on collective QOL rather than impact on just Nausea and vomiting. However this Checklist measures only impairment of Agni (G I disturbances) and is more suited to chemotherapy setting as it's known to measure some acute effects. Also being subjective checklist the subsequent psychological distress could have increased the symptomatology in these patients confounding the effects. However despite these limitations these subjective symptoms still clarify impairment in Jāṭharāgni. The

results suggest that this questionnaire captures subtleties of symptoms that need not individually impair GI function but can collectively increase distress. These symptoms so mentioned are subjective and similar to concept of symptom clusters proposed by Dodd et al. 2001, 2004).JIC is a self-reported measure to capture distress and not a diagnostic tool. It measures only presence or absence of symptoms and its severity, if present and a comprehensive tool to evaluate and asses the whole aspects of GI disturbances in its literal sense, as Western point of view is not contributing much in understanding the complex mechanism and subtler aspect of patient's problems at a time. A RCT revealed that the reduction in symptoms and improvement in quantity of meal is in concurrence with the classical texts that have elucidated ways to modulate Jāṭharāgni by diet (āhāra), medication (auoṣada) and exercise (vihāra). Āyurveda texts advocate healthy physical activity and yoga to restore balance of Jāṭharāgni(Haridāsa saṁskrutha granthamāla 106 Chap 2 Verse 10)) as a part of treatment. Studies have also shown physical activity such as exercise and yoga to improve GI symptoms in both cancer (Kerry.et al ,2007) and non-cancer populations((Taneja, Deepak et al. 2004). Āyurveda texts also describe that psychological distress is known to affect Agni imbalance, therefore the presence of these symptoms and distress give more credence to studying Agni in this current context. There are various steps to regulate the impaired Jāṭharāgni. First of these is to restore Jāṭharāgni by medication and normalizing the gastric motility. This helps in reducing the formation of "āma" or toxins that trigger the local and central nervous system which induces nausea and vomiting. Normalization of Jāṭharāgni is done by reducing stress, using yoga practices that channelize the flow of udāna and apāna vāyu and bring a balance in the prāṇa vāyu whose seat is the Jāṭharāgni.Jāṭharāgni is very important for digestion of food consumed. As Jāṭharāgni is subtle in nature it is nourished and kindled by prāṇa vāyu, samāna vāyu and apāna vāyu. Samāna vāyu

being located in the pitta sthāna is mainly concerned with metabolic process pertaining to digestion (Ramachandra's doṣa dhātu mala vignānam).It provides energy to prāṇa and is responsible for developing will power, determination and enthusiasm. Although these qualities are provided by food, it is the Jāṭharāgni that enables the food to be transformed into nutrients useful for the body. If Jāṭharāgni is weak or defective, it is not able to digest food adequately. The āhārarasa produced will be poor in quality or quantity, or both. Therefore, the dhātu's and ojas will not receive proper nourishment and will inevitably become unbalanced. In addition, all the other metabolic processes and activities, which are dependent upon the Jāṭharāgni for fuel and nourishment, will become ineffective. If Jāṭharāgni operates in a balanced way, the person stays in good health and enjoys a long life. If the function of the digestive process is impaired or unbalanced, the person becomes unhealthy and disease is generated. Thus a weak Jāṭharāgni leads directly to an imbalance of dhātu, mala and doṣa setting off a vicious cycle. This will facilitate a samāgni or normalized Jāṭharāgni state that will in turn reduce āma and reduce the symptoms of nausea and emesis. Apart from chemotherapy the antiemetic medications also may influence the Agni. Antiemetic therapy, in an effort to control vomiting, may worsen the jāṭharāgnimāndya. Hence it appears that use of Agni assessment during the management of CCINV may add value. Though there is evidence for use of non-pharmacological mind body approaches such as Yoga in reducing nausea and emesis induced by chemotherapy there is no study to our knowledge on use of Āyurveda medications or concepts in managing chemotherapy induced nausea and emesis. Pilot randomized controlled studies comparing this with conventional management strategies are necessitated. This is a holistic approach, unlike conventional approach that aims to stop vomiting by using centrally acting antagonists and reducing gastric motility. These

anti-emetic drugs are short acting and beneficial for managing acute emesis and not the delayed emesis and nausea. Chemotherapy is a prolonged treatment and the need is therefore to have sustained long term approach that helps reduce side effects and catabolic process of chemotherapy drugs and at the same time help the tissue systems to repair and rebuild using Āyurveda herbal medications and Yoga, which can modulate Jāṭharāgni. In short, this approach to Agni correction is done through vāyu. Hence yoga intervention being a comprehensive technique for regulation ofvāyu is advocated.

7.1 COMPARISON WITH EARLIER STUDIES ON YOGA IN CCINV

Our results support our earlier findings on reduction in nausea and vomiting frequency and severity with yoga intervention in breast cancer patients undergoing adjuvant chemotherapy (Raghavendra et al. 2008 Molassiotis et al. 2002 &' Raghavendra et al. 2008) However it may be pointed out that though yoga and Jacobson's relaxation did reduce nausea and emesis, the effects of yoga were more profound than Jacobson's relaxation by 3rd cycle of chemotherapy. This may be explained by the fact that there was an increase in high frequency power on HRV with stabilization of LF/HF ratio more in yoga group compared to Jacobson's relaxation signifying parasympathetic activity.

The results also offer support for decrease in self-reported depression and anxiety following yoga (Raghavendra et al, 2009 &2008) and Jacobson's intervention compared to control group. This is similar to observations made by earlier studies with Jacobson's intervention (Molassiotis et al. 2002).

The increase in percent of normal slow waves of Electrogastrogram in yoga group coincides with decrements in nausea and vomiting following 3rd cycle of chemotherapy and increase in parasympathetic vagal activity on cardiac autonomic function.

Gastrointestinal motility is reflected in gastric myoelectrical activity. There was a decrease in gastric dysmotility (bradygastria and tachygastria) in the yoga group compared to Jacobson's PMR and control intervention during chemotherapy cycles. Our results are in consonance with earlier findings of yoga intervention on gastric motility and bowel symptoms in patients with irritable bowel syndrome where in yoga has shown to increase parasympathetic cardiac reactivity and raise in gastric amplitudes at the same time (Taneja, Deepak et al. 2004).

Comparisons with one of the earlier studies in this hospital that had demonstrated the efficacy of yoga intervention in managing CCINV with antiemetics in breast cancer patients undergoing different treatment regimens (Raghavendra et al. 2006):

Their study examined the effect of an integrated yoga programme on chemotherapy-related nausea and emesis in early operable breast cancer outpatients. Sixty-two subjects were randomly allocated to receive yoga (n = 28) or supportive therapy intervention (n = 34) during the course of their chemotherapy. Both groups had similar socio-demographic and medical characteristics. Intervention consisted of both supervised and home practice of yoga sessions lasting for 60 min daily, while the control group received supportive therapy and coping preparation during their hospital visits over a complete course of chemotherapy. The primary outcome measure was the Morrow Assessment of Nausea and Emesis (MANE) assessed after the fourth cycle of chemotherapy. Secondary outcomes included measures for anxiety, depression, quality of life, distressful symptoms and treatment-related toxicity assessed before and during the course of chemotherapy. Following yoga, there was a significant decrease in post-chemotherapy-induced nausea frequency (P = 0.01) and nausea intensity (P = 0.01), and intensity of anticipatory nausea (P = 0.01) and anticipatory vomiting (P = 0.05) as

compared with the control group. There was a significant positive correlation between MANE scores and anxiety, depression and distressful symptoms. In conclusion, the results suggesting a possible use for stress reduction interventions such as yoga in complementing conventional antiemetics to manage chemotherapy-related nausea and emesis. Also studies suggested the beneficial effect of yoga in cancer chemotherapy patients (Raghavendra et al 2008, Vadiraja et al, 2009, Raghavendra et al, 2009, Cohen 2004, Raghavendra et al 2007, Buffart et al, 2012, Harder et al, 2012).But none of them were compared with Jacobson's Relaxation technique and standard emetic guidelines.

7.2 CAM THERAPIES FOR CCINV

Studies reviewed show that complementary and alternative medicine and mind/body approaches like hypnosis, progressive muscle relaxation training with guided imagery, music therapy, acupuncture, acupressure, systematic desensitization, biofeedback and distraction are useful in reducing nausea and emesis either alone or in combination with anti-emetics and anxiolytic medications (Rhodes and Daniel 2001) and. (Mundy et al. 2003). Of these, relaxation with guided imageries have been studied extensively and has shown to reduce duration and frequency of both acute and delayed nausea and emesis following chemotherapy in subjects with poor control of nausea and vomiting.(Burish and Tope, 1992),(Arakawa, 1997) and (Molassiotis,2000). Most of these techniques reduce anxiety, physiological arousal and psychological distress in cancer patients through stress reduction(Morrow and Rosenthal, 1996) A growing interest in the use of these therapies reflects a need for more holistic approach to cancer treatment (Cassileth, 1999)

7.3 POSSIBLE MECHANISMS

Earlier researchers like Darmani, (2010) .hypothesized that possible mechanism of inhibition of gastrointestinal motility resulting in reduction of gastrointestinal motility in CCINV could be by (i) local -direct relaxant effect on smooth muscles of GIT and/or (ii) central- control inhibition of excitatory neural pathways or by activation of inhibitory pathways. All factors acting at central as well as local level might be bringing about normalizing changes as seen with an increase in percent of normal waves following yoga intervention in our study.

7.4 LOCAL FACTORS INVOLVED IN CCINV

Ingestion of toxin, traumatic events, adverse drug reactions, and motion can all result in nausea and emesis. Chemotherapeutic agents can cause emesis through afferent input at a number of different sites, involving different mechanisms. Chemotherapeutic agents are toxic to EC lining the GI mucosa and stimulate them to release neurotransmitters, such as dopamine, serotonin (5-HT), substance P (SP), acetylcholine, histamine, and gamma-aminobutyric acid (GABA) (Hesketh, 2008; Leslie and Reynolds, 1993; Navari, 2009; Rudd and Andrews, 2005). These neurotransmitters bind to the appropriate receptors on the abdominal vagal afferents (Blackshaw et al. 2007; Burke et al., 2011; Lesurtel et al. 2008), hence activating them, which then conduct the stimuli to the dorsal vagal complex consisting of emetic/VC, the area postrema (CTZ) and the NTS. These sensory inputs are then integrated resulting in the activation of the emetic response (Hesketh, 2008). Another possible source of afferent input inducing emesis involves the CTZ (Borison, 1989; Miller and Leslie, 1994), which is sensitive to chemical stimuli from drugs (Rang, Dale, Ritter, and Flower, 2007). The blood-brain barrier located in CTZ is permeable to circulating mediators, thereby, allowing them to directly interact with the VC (Rang et al. 2007) and resulting in emesis.

7.5 PSYCHO PHYSIOLOGIC DIMENSIONS OF CCINV

The gastrointestinal tract is sensitive to emotion. Anger, anxiety, sadness, elation, all of these feelings (and others) can trigger symptoms in the gut. The brain has a direct effect on the stomach. For example, the very thought of eating can release the stomach's juices before food gets there. This connection goes both ways. A troubled intestine can send signals to the brain, just as a troubled brain can send signals to the gut. Therefore, a person's stomach or intestinal distress can be the cause or the product of anxiety, stress, or depression. That's because the brain and the gastrointestinal (GI) system are intimately connected — so intimately that they should be viewed as one system. Psychosocial factors influence the actual physiology of the gut, as well as symptoms. In other words, stress (or depression or other psychological factors) can affect movement and contractions of the GI tract, cause inflammation, or make it more susceptible to infection. A review of 13 studies showed that patients who tried psychologically based approaches had greater improvement in their digestive symptoms compared with patients who received conventional medical treatment.[Miller , Leslie , 1994, 2001

7.5.1 Central mechanism – ANS tone

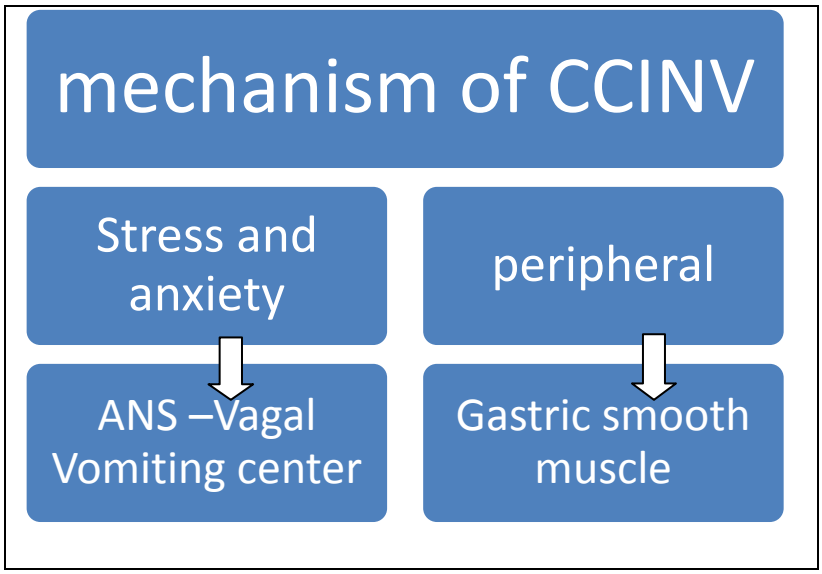
Studies have shown that some of the side effects that develop following chemotherapy may be partly psychological rather than purely pharmacological in nature. (Burish and Tope , 1992) Nearly 70% of patients who experience anticipatory nausea and emesis attribute these side effects to a psychologic etiology (Morrow, 1982). This may be because the information from the vomiting center to higher brain centers is involved in the perception of nausea and vice versa (Hawthorn 1995). Also, it has been hypothesized that CCINV may manifest because of disturbed brain–gut interaction at ANS, enteric nervous system (ENS), vagal/ gastric irritation of gut musculature or biochemico-physical milieu of luminal contents (Mayer, 2006). A relationship between autonomic dysfunction and CCINV has been reported (Morrow 1992 and Bellg et al,

1995).Basal ANS tone has been shown to be related to anticipatory or conditioned nausea induced by anti-cancer chemotherapy(Kvale,et al. 1991).

7.5.2 ANS and anxiety in CCINV

This is in tune with what is expected, since anxiety is known to exacerbate and cause anticipatory symptoms which may be mediated in part through autonomic dysfunction. Various studies have shown risk factors such as motion sickness, vomiting related to particular foods, pre-treatment anxiety and expectations (Jacobsonet al. 1988 and Morrowet al. 1991) to have a strong predisposition for post chemotherapy and anticipatory nausea and vomiting and these can further exacerbate the responses to conditioned stimuli in these subjects (Matte et al. 1987).

Fig. 7.1: Mechanism of CCINV



The link between stress and chronic disease is mediated by endocrine pathways of the sympathetic nervous system (SNS) including the hypothalamus-pituitary-adrenal (HPA) axis (Cohenet al. 2007) (Rosmond and Bjorntorp 2000).

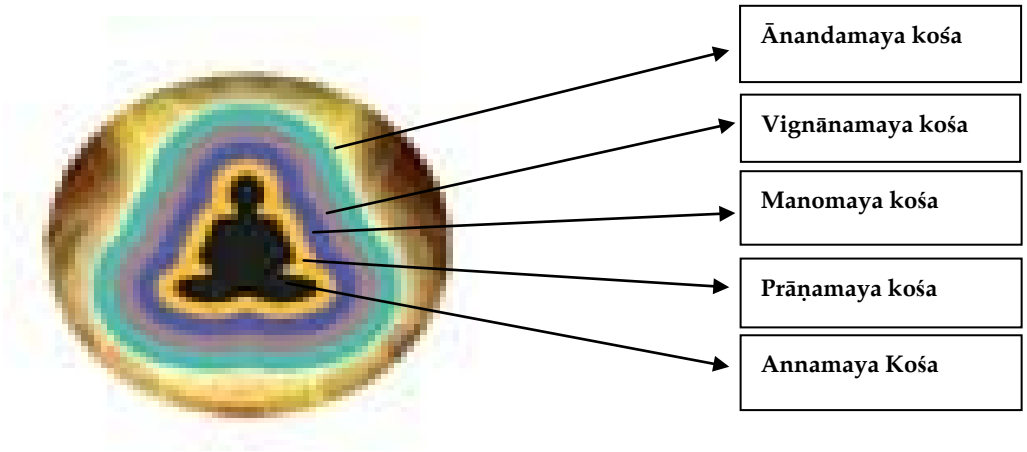
Studies suggest that, changes in parasympathetic activity may mediate symptoms associated with nausea. For example, changes in parasympathetic outflow may be of practical use in identifying the transition from the prodromal phase (including nausea)

to the expulsive phase of the emetic reflex (Andrews and Davis, 1995) and (Andrews and Davis, 1993). Basal ANS tone has also been shown to be related to anticipatory or conditioned nausea induced by anti-cancer chemotherapy (Kvale et al. 1991). This is expected as anxiety is known to exacerbate and cause anticipatory symptoms and which may be mediated in part through autonomic dysfunction. Various studies have shown risk factors such as motion sickness, vomiting related to particular foods, pre-treatment anxiety and expectations. (Jacobson, et al. 1988) and (Morrow et al. 1991) to have a strong predisposition for post chemotherapy and anticipatory nausea and vomiting and these can further exacerbate the responses to conditioned stimuli in these subjects (Mattes et al. 1987). Therefore, these strong relationships between psychosocial variables, autonomic dysfunction and nausea and emesis justify the need for integrating mind body therapies with pharmacological interventions in managing treatment related nausea and emesis. (Schwart et al. 1996). Studies have reported that no single neurotransmitter appears to be responsible for all CCINV (Grunberg and Ireland 2005), let alone for Acute Nausea Vomiting -ANV. In addition, though the inhibition of some of these pathways results in reducing vomiting, the same is not true for reducing nausea. This suggests that the induction of nausea and vomiting may involve different pathways and mediators. Moreover, post-treatment CINV occurs due to stimuli to the CTZ and the VC regions while ANV occurs when the VC is activated by perceptive stimuli which are generated by personal thought, feelings or sensory stimuli associated with the chemotherapy (Duigon 1986). Though ANV is less frequent than post-treatment CINV, it represents a significant problem as it leads to more discomfort in cancer patients undergoing chemotherapy and is usually more difficult to control than acute CINV or DNV (Grunberg, 2007). Better understanding of the mechanisms of different types of CINV may help in the development of additional effective antiemetic drugs.

7.5.3 The yoga model for causation of cancer and CCINV

Yoga considers the living human body as a flux of continuous changes that is programmed to live a full lifespan of about a century in perfect health. As man goes through the ups and downs of life (be it exposure to external onslaughts like injury or infection or toxic drugs, or emotionally challenging situations it sets off an imbalance. The scriptures explain that these imbalances occur due to lack of mastery over mind which is the beginning of any mind-body disease. According to one of the major upaniṣad called the taittiriya upaniṣad (Gambhirananda, 2010), the human system consists of five components [pañca kośa] comprised of the physical body (Annamaya Kośa), subtle energy or Prāṇa (prāṇamaya kośa), instinctual mind (Manomaya kośa), intellectual or discriminative mind (Vignānamaya kośa) and bliss-full silent state (Ānandamaya kośa)

Fig. 7.2: Five Sheaths Pañca kośa



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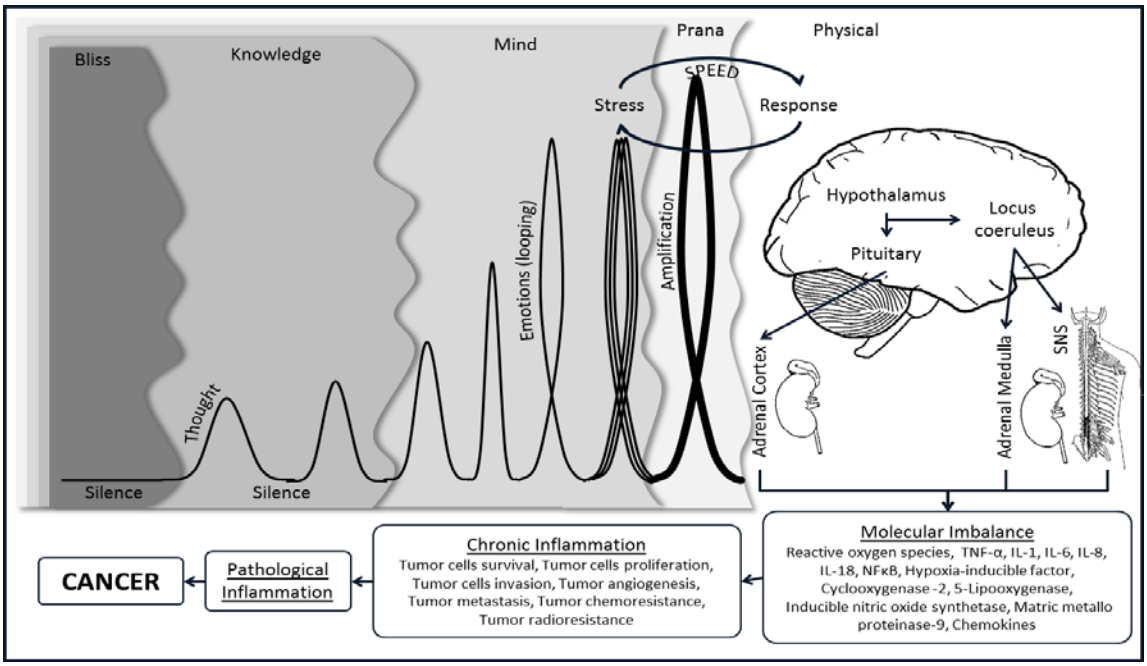
Health is a state of complete mastery that promotes living in Ānandamaya kośa which in turn influences Vignāna. This is a state of complete contentment and freedom from all distress and disease (Ch2 V12)(Easwaran, 1973). Sage vasiṣṭa describes the progression of an imbalance that is created by persistent stress which may result in cancer (and/or other lifestyle related disorder) (Ch9 V82-117)(Venkatesananda & Chappel, 1984).

Fig. 7.3: Model of cancer according to yoga texts copyright Dr Amrit Ram. SVYASA University



The imbalance due to uncontrolled speed (udvega) of suppressed emotions when unchecked results in an imbalance and percolates into prāṇamaya kośa. This is detectable as disturbed pattern of breathing (increased rate and irregular rhythm) and poor digestion. As this imbalance and loss of mastery goes on for some time it becomes an involuntary habit, a reflex. Chronic constipation or irritable bowel (constipation and diarrhoea), fatigue and generalized body aches are the other general (non-specific) manifestations at this level. When unattended by correcting the imbalance at the root In summary, the yogic model proposes that cancer is due to repetitive onslaught by uncontrolled thoughts (suppressed emotions) at the mind level (Manomaya kośa) which causes excessive prāṇa activity and manifests as violence (inflammation) at annamaya kośa to show up as cancer. Chemotherapeutic drugs add on to the problem to increase the imbalances and result in CCINV. Thus, according to yoga cancer may be considered as ādhija vyādhi (imbalance induced by life style) and the chemotherapy induced vomiting is anādhija vyādhi (imbalance induced by external agents) and

chemotherapy induced nausea as aggravation of ādhi (psychological stress, anxiety) - yoga vasishta chapter 2. cause (the Manomaya and Vignānamaya kośas) the process continues and localizes to a specific zone in the physical body (Annamaya kośa). Thus, the uncontrolled rush of prāṇa (vital energy), results in uncontrolled electro-chemical process in the physical body, the annamaya kośa. This appears to mean that the physical fight (tissue inflammation) is a reflection of the violence or fight in the mind. We know today that inflammation is a feature of cancer. Thus, the uncontrolled excessive prāṇa (subtle energy) flow seems to cause the changes in the molecular level that goes on to alter the apoptotic programming resulting in immortal cells and perpetuation of cancer cells **[Figure 7.3].** Further, the texts go on to describe that the localization of the disease (cancer) depends on external (insult by carcinogenic agents, trauma, toxins, and infections) or internal (genetic) factors.

7.6 YOGA THERAPY FOR CCINV-MECHANISM

In the present study, the reduction in severity of delayed nausea and emesis in yogic intervention group and Jacobson's group indicates reduction in excessive motility, which is found in patients with nausea and emesis (Geldof, et al ,1986).It has been reported earlier that though visceral hypersensitivity in nausea is both centrally and peripherally mediated**(**F De Ponti et al ,2004),peripheral sensory modification at enteric or spinal level might be an effective therapy. Thus we propose that yogic intervention may be acting at central as well as peripheral/visceral level thereby bringing about subjective improvement in clinical symptoms.

Yoga as a complementary modality is being practiced increasingly in both Indian and western population. Yoga practices have been used for therapeutic benefit in numerous health care concerns such as asthma (Nagarathna&Nagendra, 1985) , diabetes

(Sahay&Sahay, 2002), hypertension (Sainani, 2003), , heart disease .(Jayasinghe , 2004), musculoskeletal disorders (Raub, 2002), cancer (Cohen et al , 2004), and others in which mental stress. (Gimbel, 1998) and (Bijlani ,2004), was believed to play a role. These practices include several techniques such as āsana (postures done with awareness), praṇāyāma (voluntarily regulated nostril breathing), yoga nidra (guided relaxation with imagery) and meditation, which promote physical wellbeing and mental calmness. These practices are known to build inner awareness and attention of mental phenomena. This is thought to alter the perceptions and mental responses to both external and internal stimuli, slow down reactivity and responses to such stimuli and instil a greater control over stressful situations. This could be particularly useful in cancer patients who perceive cancer as a threat. Recent randomized Controlled studies using meditation and yoga components have found beneficial effects in terms of improved affective states, decrease in mood disturbance, stress symptoms, disturbed sleep, improved quality of life and benefits in terms of improved immune responses in early breast (Speca et al. 2000) and (Targ& Levine , 2002) and prostate cancer patients (Carlson et al. 2003). . Most of these studies involve heterogeneous cancer population at varying stages of their disease and treatment and evaluate quality of life and psychosocial outcomes. One of the earlier studies in this hospital demonstrated the efficacy of yoga intervention in managing CCINV with antiemetics in breast cancer patients undergoing different treatment regimens (Raghavendra, et al. 2006). Several studies mentioned above have demonstrated the effectiveness of attention diversion strategies for the reduction of stress and pain. It is likely that relaxation and deep somatic restfulness induced by yoga practices may reduce anxiety; physiological arousal and stress associated with chemotherapy and prevent exacerbation of such responses induced by post chemotherapy nausea and vomiting thereby reducing the

general feelings of distress. By the practice of integrated yoga designed to reduce the imbalances at all levels allows one to be established in blissfulness accompanied by right knowledge or awareness. Yoga nurtures the ability to manipulate the laws of nature within the body and outside the body (Ch1 V4 patanjali yoga sutras Taimini, 1999).

7.6.1 Annamaya Kośa Practices

The yoga postures could have helped reduce muscular contractions in the gastrointestinal tract (Taneja et al. 2004) that accompany post chemotherapy nausea and vomiting or may have decreased the sensitivity of chemoreceptor trigger zone in the stomach lining that may induce vomiting response (Borison and McCarthy,1983) It has also been seen that maintenance in āsana leads to pressure changes in visceral organs, which restore the normal functioning of the abdominal viscera. These pressure changes are expected to stimulate visceral afferents and thus help to bring about a change in neural, visceral, and emotional activity at the highest level.

Rest effect

According to yoga, relaxation is the healer for all ādhija vyādhi. Yoga postures, though appearing to be similar to physical exercises, have several fundamental differences. *Yogāsanas* (physical practices) bring about muscle stretches that are maintained with ease and effortlessness.

स्थिरसुखमासनम्॥ प यो सू। २। ४६॥

sthirasukhamāsanam ।। pa yo sū । 2 । 46 ।।

The posture should be steady and comfortable.

Sage *Patanjali* recommends two clear instructions to be followed while practicing *āsana* in order to achieve the main goal, which leads to mastery over the modifications of the mind.

Conscious relaxation of the stretch *(prayatna śaithilya) a*nd Experiencing the unlimited expansion *(anantasamāpatti)in the* part that is stretched or pressed that offers deep local rest to the stomach area in śaśāṅkāsana and pavanamuktāsana

प्रयत्नशैथिल्यानन्तसमापत्तिभ्याम्॥ प यो सू। २। ४७॥

ततो द्वन्द्वानभिघातः॥ प यो सू। २। ४८॥

prayatnaśaithilyānantasamāpattibhyām ।। pa yo sū । 2 । 47 ।।

tato dvandvānabhighātaḥ ।। pa yo sū । 2। 48 ।।

It results in relaxation of effort and the meeting with the infinite.

From then on, there are no botheration from the dualities like happiness and distress, heat and cold.

Relaxation sessions in Śavasana posture incorporated within the 25 minutes yoga module ensured this progressively increasing relaxation as one moved on from one set of āsana to the next. Thus yoga postures offer voluntary introspective relaxation of the stomach area and releases the local blocks due to exaggerated activity of prāṇa that had resulted in vitiated vāta and pitta.

7.6.2 Mechanism of yoga for CCINV - prāṇamaya kośa

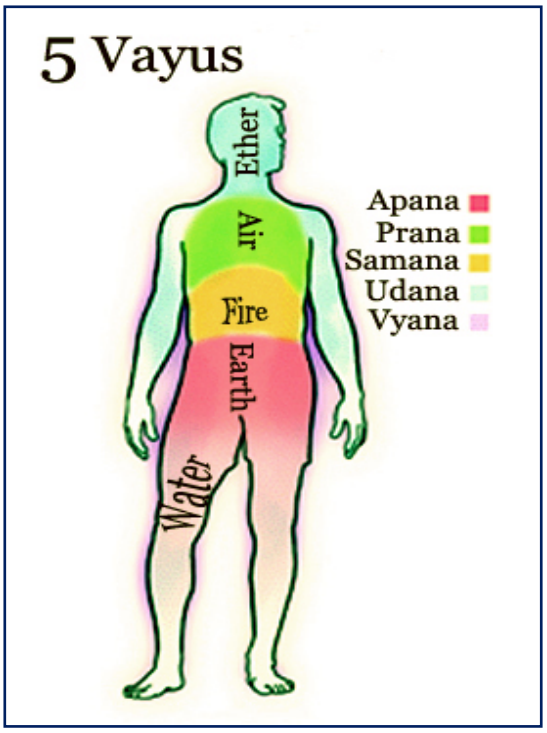
In the hypothesized model describing the process of evolution of CCINV based on Āyurveda and yoga, we have included of role of disturbances in the five aspects of Prāṇa that goes on to produce nausea. Prāṇa the life energy is not the material electromagnetic energy spectrum known to modern science. All these energies like electricity, sound, light, radio, x-ray, etc. belong to annamaya kośaas they are bound by

energy laws. The Prāṇa described here is subtler than that. It does not follow the physical energy laws. It is described as that which can increase or decrease by itself without any external agency. A uniform harmonious flow of Präna to every cell of the annamaya kośa keeps them alive and healthy.

Prāṇa is in continuous flux moving into different areas of the body depending on demand. For e.g.whenone performs more brain work more Prāṇaflows to the brain region, when one walks more Prāṇa flows to the lower Limbs, etc. If the Prāṇa flow to any organ increases inadvertently and without control, it can lead to dysfunction of that organ at the Annamaya kośa.

According to Āyurveda [ācārya caraka] this is referred to as vāta. *The description of the functions of* vāta *says 'All movements are due* vāta *and hence it is called the 'Prāṇa' of all living beings'. (*caraka *Sū. Ch 18 V 118).* In general, the functions ascribed to 'vāta' are: Control and coordination of all functions of different parts of the body, initiation of all movements, regulation of psychological processes, initiation of all activities of sense organs, transmission of different sensations, production of speech, secreto- motor functions in the gut, expulsion of wastes from the body, control of respiration etc. (caraka.Sū.Ch 12 V 8). Prāṇa flows through subtle channels called Nädis (rasavaha śrotas according to Āyurveda or meridians according to Chinese medicine)resulting in all physiological activities. There are five directions in which the Prāṇa flows within the body to carry out different functions and these are called pañcaPrāṇa s based on the direction in which they flow.

Fig. 7.4 : 5 directions of Prāṇa



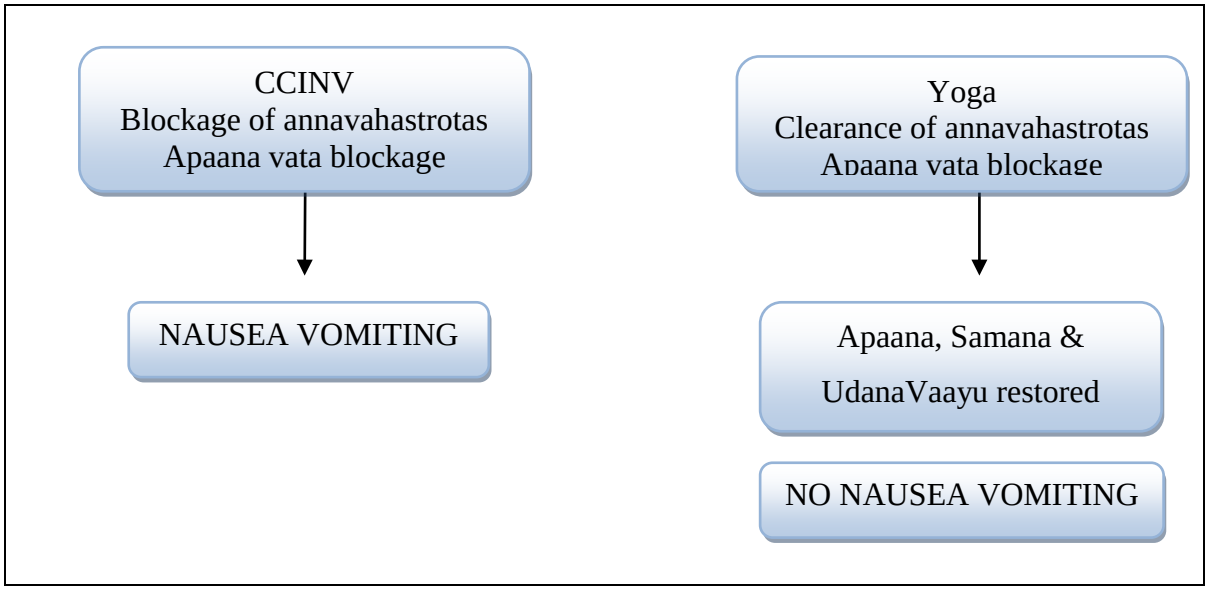
The Prāṇa responsible for breathing movement is called 'Prāṇa' or mukha prāṇa. Āyurveda describes the functions ofPrāṇa vāyu which is situated in head as that movement which is responsible for the control over intellectual functions, cardiovascular functions, sense organs, psychological activities, respiration, and reflex activities like sneezing, belching and deglutition(Aṣṭāṅga hridaya.Sū. Ch 12 V 5).

The downward force called Apāna is responsible for functions like defecation, urination, menstruation, ejaculation, parturition etc. Udāna is responsible for upward activities like vomiting, belching, coughing and spiritual evolution of the soul. Samāna is responsible for proper digestion and balancing the Prāṇa and apāna.Āyurveda adds that the active site of 'Samāna' is in the gastro intestinal tract. It performs the functions like reception of food, its digestion through the activation of 'Agni', its division into useful and waste parts and its onward propulsion (Aṣṭāṅga hridaya Sū. Ch 12 V 8).Agni in the digestive tract is nourished and kindled by Prāṇa, Samāna and

apānavāyu s in the process of digestion.Vyāna is responsible for all activities in the periphery like nerve impulses, blood circulation, and cellular activity in all the cells. A balance between all these five directionalflow of Prāṇa is health, and imbalance is ill health. In the model we have proposed that the chemotherapy induced agnimāndya results in blockage of apānavāta (downward flow) that pushes the Prāṇa in the upward direction by activating Udāna resulting in presenting nausea feeling and vomiting. Thus CCINV is a natural programmed way to get rid of the excessively activated stock of Prāṇa(induced by stress from the subtler layer the manomaya kośa.) either by vomiting (Udāna) if not through diarrhoea(apāna excess). Thus yoga proposes that the aim is to reduce the overall heightened activity of Prāṇa which has to be done by reducing the excessive demand from the brain to carry out the violent thought processes that go on incessantly during or distressful emotional responses such as anxiety or fear of chemotherapy.

praṇāyāma formed a major component of the yoga practices taught to these patients praṇāyāma is defined as a yoga technique to get mastery over the excess release of Prāṇa through slowing down the breathing rate with deep awareness. Thus we planned the practice of praṇāyāma with emphasis on slow abdominal breathing and bhramari practiced several times in the day to slow down the overall Prāṇa activity in general and more so in the Udāna zone. Thus we propose that the practice of praṇāyāma would have resorted the balance of apāna udāna and samāna Prāṇa activity.

Fig. 7.5 : Prāṇa imbalance in CCINV corrected by yoga



7.6.3 Manomaya kośa practices of yogafor CCINV

Yoga intervention is a type of mind body intervention with profound behavioural modification by reducing anxiety and depression (that can exacerbate these GI symptoms). The calming effect of the relaxation therapies can reduce sympathetic responses to stress and usher in reduction of excessively activated parasympathetic response to restore homeostasis in the system (Matteoli, 2013), the stabilising effect of yoga that is meant to bring about

7.7 MECHANISMS OF CCINV – ĀYURVEDA PERSPECTIVE

Recent studies report very interesting observations that were described in Āyurveda several thousand years back. A recent report in nature science said: ‘The gut and the brain are closely connected, and this interaction plays an important part not only in gastrointestinal function but also in certain feeling states and in intuitive decision making. Recent neurobiological insights into this gut–brain crosstalk have revealed a complex, bidirectional communication system that not only ensures the proper maintenance of gastrointestinal homeostasis and digestion but is likely to have multiple effects on affect, motivation and higher cognitive functions, including intuitive decision

making. Moreover, disturbances of this system have been implicated in a wide range of disorders, including functional and inflammatory gastrointestinal disorders, obesity and eating disorders'. (Emeran and Mayer2011*)*

7.7.1 Gross and subtle phases of digestion

According to Āyurvedathe process of digestion takes place in two steps, the Avasthāpāka and Niṣṭhāpaka. Avasthāpāka phase refers to the gross digestive process that breaks the complex food ingredients to smaller particles by the digestive juices secreted in the successive parts of the alimentary canal. This refers to the process of digestion in different parts of digestive system as understood by modern physiology. Niṣṭhāpaka phase refers to formation of nutrients after the completion of the chemical processes of Avasthāpāka (Caraka Sü Ch 26 V 61-64). [Caraka Grahaṅichikitsa Ch 15, V 7-9] .Both these processes need Agni (the bio energy) for carrying out the digestive processes. Breaking down of the complex food particles into simpler forms by the secretion of juices and its transformation is done by Jāṭharāgni. Jāṭharāgni is also refered to as 'Pācaka Pitta' (Aṣṭāṅga hridaya Sū. Ch 12 V 11). Body nutrients are further transformed to absorbable nutrients through bhūtāgni. The absorbed chemicals end up as sāara (nutrients) and Kitta (feces, the waste products).

The further process of absorption and the cellular metabolism i.e. the Niṣṭhāpaka is carried out by subtler angis. Bhūtāgni, the latent energy of the five basic elements (pañca mahā bhūta) and dhātvāgni the potential energies of the seven tissues (sapta dhātu) are involved in this. These two Agni's are also dependent upon Jāṭharāgni for its proper functioning i.e. normal metabolism .Hence normal functioning of Jāṭharāgni plays an important role in the maintenance of Health.

7.7.2 Relation betweenAgni and prāṇavāyuin digestion

Jatharägni is subtle in nature and nourished and kindled by prāṇavāyu in the process of digestion, the Mukha prāṇavāyuin the mouth and the oesophagous, Samānaprāṇavāyu in the stomach and small intestine and Apāna prāṇavāyu in the rectum and anal canal. The food mixed in the mouth conveyed by prāṇavāyu to the gastro duodenal region where it is acted upon by samānavāyu. Samānavāyu which is situated near antarāgni admits food, disintegrates it, and assimilates. apānavāyu discards the waste that is formed after completion of the digestive process in the intestines(Caraka Grahani CikitsaCh 15 V 8). Samāna vāyu works in conjunction with Prāṇa, Apāna and vyānavāyu. It is closely connected with Jāṭharāgni, which it regulates according to the circumstances.

7.7.3 Impaired Jāṭharāgni in CCINV

Impaired Jāṭharāgni (Mandāgni –Hypo/Hyper) results in abnormal digestive processes. The undigested food or the non-simplified nutrients leads to formation of endotoxins (Āma); accumulation of āma is the root cause for all diseases. Impaired Jāṭharāgni manifests as one of the major symptoms (rûpas) namely Anorexia. (Caraka chi vi Ch 4 V8). In CCINV, the impaired Jāṭharāgni due to the chemotherapy results in excess formation of āma which is neither digested nor excreted, this along with the chemotherapy drugs (tīkṣṇa auoṣadha), the fear of the disease (rogabhaya) and the depression (Caraka chi Ch 20 V7) affect the entire gastrointestinal tract (GIT-Mahā Śrotas). Also, the tīkṣṇa auoṣadha vitiates the circulatory system (raktadhātu) which in turn causes aggravation of pitta doṣa. Fear and depression are due to aggravation of prāṇavāyu. This impact on GIT affects the Samānavāyu0and in turn further

aggravates the Jāṭharāgni māndhya. Further the Udānavāyuthat has its seat in Thorax (Uras) gets affected.

7.7.3.1 Correction of impaired Jatharāgni and prāṇavāyu in CCINV through yoga

Nausea and Anorexia are directly related to each other (Schwartz et al1996), and correction of anorexia reduces nausea. We have seen how the practice of postures (Āsanas) increases the digestive power and practice of praṇāyāma regulates the prāṇavāyu. Hata yoga Ch 2 V17, V 19 Regulation of samāna prāṇa vāyu (subsequently Jatharägni) is done through regulation of prāṇavāyu(Caraka chi Ch 28 V3,4)by yoga intervention (Haṭha yogaCh 2 V17, 19) (Aṣṭāṅga hridaya Ch 2 V 10).Though in yoga and Āyurveda the treatment approaches are different because of the methods adopted, the primary objectives of treatment approach are same. I.e. vāyu niyantraṇa (regulation of vayu) and reestablishment of Agni is the outcome of yoga practice. (Caraka chi Ch 28 V6-8, V220). Āyurveda and yoga understands importance of psychic influence on the somatic response of the body. We also know that the psychic influence is measurable in terms of neuro-endocrine and immune responses and the existence of directionally communicating psycho neuro-endocrine-immune axis. (Blalock J .E (1987)"New concepts in endocrinology: Neuro endocrine & Immune system interactions" Year book of endocrinology, Pages 15-18) The therapeutic approach applied here is restoration of health and rehabilitation (Caraka Chi Ch 1 V3) by adopting naiṣṭikacikitsa through yoga.

7.7.3.2 Summary of the mechanism of yoga and Āyurveda for CCINV

In summary the Āyurveda concepts of Agni māndya resulting in CCINV and the evidence from this study offer support from traditional texts for the psychological pathway of anticipatory nausea and emesis that has been recognized by modern

scientists (Morrow 1982) . The intense disturbances produced by chemotherapy, can further add up to the psychological distress and majority of these patients show adjustment disorders with symptoms of mixed anxiety and depression. (Gogne, Khandelwal et al. 2011). Activation of the vomiting centre may occur as the result of afferent input from drugs, such as chemotherapeutic agents, motion, smells, sights, situations, and emotions, as well as from gastrointestinal input. (Hawkins and Grunberg 2009).

Also it is seen that changes in parasympathetic outflow may be of practical use in identifying the transition from the prodromal phase (including nausea) to the expulsive phase of the emetic reflex (Andrews and Davis 1993; Andrews and Davis 1995). Basal ANS tone has also been shown to be related to anticipatory or conditioned nausea induced by anti-cancer chemotherapy (Kvale, Hugdahl et al. 1991)

An earlier study on breast cancer patients has shown yoga to help in reducing post chemotherapy nausea and emesis in early breast cancer patients (Raghavendra, Nagarathna et al. 2006).Beneficial effects of yoga in terms of improved affective states, decrease in mood disturbance, stress symptoms, disturbed sleep, improved quality of life and benefits in terms of improved immune responses in early breast (Speca et al. 2000) and prostate cancer patients (Carlson et al.2003)The yoga postures could also help to reduce muscular contractions in the gastrointestinal tract (Taneja et al. 2009) that accompany post chemotherapy nausea and vomiting or may decrease the sensitivity of chemoreceptor trigger zone to vomiting response –stimuli (Barison 1983).

Chapter-8

APPRAISAL

8.1 SUMMARY AND CONCLUSIONS

8.1.1 Summary of all Results	
Study 1 Development of Jāṭharāgni checklist	
Jāṭharāgni Impairment Checklist (JIC) based on Āyurveda and yoga developed. Content validity established by expert opinion. Divergent validity established by comparison with Functional Life Index of Emesis. Reliability established with Chronbach's Alpha of 0.79.	
Study 2: Effect of integrated yoga on CCINV	
Variables	**Results**
Primary outcome variable : Jatharāgni Impairment Check list	Within subjects effect was significant for time (P<0.001) only. **Within yoga group** JIC Score increased after first cycle of chemotherapy (p<0.001 between C0 and C1). Significant **decrease** in JIC Score after second cycle of chemotherapy (C1 and C2 =p=0.001). **Within Jacobson's PMR group** JIC Score increased after first cycle of chemotherapy (p<0.001 between C0 and C1). JIC Score increased after third cycle of chemotherapy (p=0.004 between C0 and C3). **Within Control (Waitlist) group** Significant increase in JIC scores between baseline and C0 vrs C1 D7 of first cycle (p<0.001) **Between subjects effect** was not significant (p=0.31) for total Agni score following all three chemotherapy cycles.
Quantity of meal	Significant improvement in quantity of meal at C3 in yoga group compared to Jacobson's group and controls (r=0.23, p=0.02).

Nausea severity	Acute and delayed nausea severity decreased significantly more in the Yoga group as compared to the control group (p=0.001) and Jacobson's group (p=0.004) after the 1st cycle of chemotherapy.
Psychological tests	Significantly better decrease in anxiety and depression scores in the yoga (p=0.03) and Jacobson's groups (p=0.004) as compared to controls. Significant decrease in self-reported anxiety and depression in Yoga (p=0.03) and Jacobson's relaxation (p=0.004) compared to control group at the C3 time point.
Autonomic test - HRV	Better decrease in the low frequency (LF) and high frequency (HF) bands) ratio (p=0.06, between groups) in Yoga group compared to control group after C3 time point.
Autonomic test - EGG	Significant decrease in bradygastria (p=0.002) and tachygastria percentage (p=0.03) in Yoga group compared to Jacobson's and control group evident after the third cycle (C3 time point.

8.1.1.1 *Study 1*

This study offers a model of evolution of CCINV according to Āyurveda. This study offers a validated reliable measure of Agni based on the unique concepts from Āyurveda that describes the process of evolution of CCINV. It has developed and standardized a checklist to measure Jāṭharāgni impairment. Checklist was developed on the basis of symptoms explained in classical texts and expert's opinion and were standardized, by administering them, on both, non-cancer patients taking Āyurveda treatment and those with cancer on chemotherapy. The checklist was able to show that Yoga therapy reduces Agni impairment.

The results suggest that this questionnaire-JIC captures subtleties of symptoms that need not individually impair GI function but can collectively increase distress.

8.1.1.2 *Study 2*

This is the first prospective randomized controlled study to compare yoga with an active control like Jacobson's relaxation that has proved to be useful in reducing nausea and emesis. Overall the study supports earlier observations of the beneficial effects of yoga in reducing nausea and emesis.

Although the results after yoga practices were similar to Jacobson's relaxation, the benefits of yoga were more profound when done for a longer time as seen with differences after 3rd cycle of chemotherapy.

The restoration of normal gastric motility and stress reduction could be one of the mechanisms by which yoga could reduce CCINV in subjects undergoing chemotherapy.

It has shown the effect of yoga in CCINV in chemotherapy naïve subjects with solid malignancies and lymphomas receiving highly or moderately emetogenic chemotherapy.

The results of the RCT study:

Yoga as a both mind body intervention and stress management intervention can help modulate Agni by reducing anxiety or reducing gastro paresis.

In short we can conclude that Yoga therapy acts as a complimentary treatment in reducing Jāṭharāgni impairment dealt in this study as chemotherapy induced nausea and vomiting and other related GI symptomatology in cancer patients undergoing chemotherapy.

8.2 STRENGTHS

- Study highlights aspects of both acute and delayed nausea that were not studied earlier.
- The questionnaires used in this study are more robust and are at specific time intervals compared to earlier study which elicited responses overall during chemotherapy using morrow assessment of nausea and emesis.

- The study highlights the fact that both yoga and Jacobson's relaxation are useful in reducing nausea and vomiting and more so yoga therapy for the delayed nausea and vomiting which remains an important problem even today in spite of advancements in antiemetic therapies.
- The results of this study are more apt for the clinical setting as standard antiemetic guidelines were followed as compared to earlier study wherein subjects were poorly controlled for nausea and emesis with a different antiemetic regime.
- This is the first study that has shown the benefits of yoga and Jacobson's relaxation on CCINV using an objective test of gastric autonomic function.
- This is the first study that has shown the benefits of yoga and Jacobson's relaxation on CCINV using an Āyurveda based assessment tool of Agni assessment.

8.3 LIMITATIONS

- One of the major limitations of the study was that the yoga or Jacobson's relaxation program could not be done in supervised settings. However we had good adherence to both the interventions as we had provided video CDs of yoga and Jacobson's progressive muscle relaxation and trained them earlier on this intervention.
- Secondly, the Electro Gastro Gram recording was done with AD instruments 16 channel polygraph which did not have the software for real time EGG recording. We had to use a filter to remove noise due to Electro Cardio Gram inputs to derive the EGG data.
- Different types of antiemetic regimens used could have had confounding effects and this need to be analyzed as subgroups in future studies on larger samples.
- This study recruited patients with many cancers taking the inclusion criteria based on the type of chemotherapeutic agent used and its impact on NV. As the progress and response to yoga may vary in different types of cancer in different organs future studies need to focus on any one type of antiemetic therapy.

8.4 APPLICATIONS

- As this study confirms our earlier observations of the benefits of yoga for CCINV it is recommended that this module of yoga may get incorporated in the standard protocol of management. All centers may introduce yoga for all patients undergoing treatment to give them the benefit of both the antiemetic drugs and mind body intervention.
- Our results offer further support for the effects of Jacobson's progressive muscle relaxation to reduce nausea and emesis.
- Yoga can be used as an effective intervention in chemotherapy day care and outpatient settings to help patients manage nausea and vomiting due to chemotherapy.

Yoga is one such intervention, which is gaining popularity among the Indian masses and oncology clinics could adopt these interventions by training nurses involved in cancer care. Approximately 56% of the cancer patients in a developing country like India take recourse to complementary and alternative therapies with an intention to gain benefit and not because of dissatisfaction with conventional treatment (Gupta et al, 2002). The popular beliefs associated with these treatments have helped cancer patients to adopt healthy self-care behaviours. Use of these interventions in a hospital setting could help complement the effects of conventional antiemetics in managing chemotherapy related nausea and emesis. These interventions can be useful where there is lack of infrastructure for offering supportive care and also where subjective concerns regarding treatment related side effects are not given their due concern.

8.5 SUGGESTIONS FOR FUTURE WORK

8.5.1 Agnicheck list

- Pilot and randomized controlled studies comparing Āyurveda concepts with conventional management strategies are necessary.

- We recommend the incorporation of agni check list and other measures used in Āyurveda such as tridoṣa and āma questionnaires in studies on CCINV to validate the model portrayed in this study
- Future studies are necessary to offer stronger acceptable evidences for use of agni check list for routine use. Hence studies may be designed with the following objectives:
    - To validate if this checklist can be used in other chronic illnesses as well.
    - To look at a larger population
    - To develop ideal subscales using factor analysis.
- To conduct studies on a larger sample size for understanding the abstract and subtle concept of Jāṭharāgni impairment amenable to minute changes over time that underlies the gross symptomatology.
- To conduct studies using Agni questionnaires with or without treatment.
- To conduct studies to evaluate the benefits of Āyurveda herbs selected after on Agni assessments in management of CCINV

8.5.2 Yoga for CCINV

- Studies may be conducted to develop easier and shorter duration practices of yoga for its acceptability for universal use. CDs and booklets may be made available to both patients and therapists just like Jacobson's technique which is now made uniform and is available for use round the globe.
- More multi-center phase III randomized controlled trials on larger sample size with more objective tools are recommended to understand:
    - to enhance the evidence base for these approaches
    - Its applicability to all cultural and socioeconomic groups
    - To understand the mechanisms at molecular and psychological levels.

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APPENDIX

1. INFORMED CONSENT FORM Protocol ID: Y010810

TITLE: Comparison of effect of Yoga versus relaxation on CINV outcomes following chemotherapy

Contact Information:

Dr. Raghavendra Rao. M

Principal Investigator

44-45/2, Bangalore Institute of Oncology

2nd Cross, Rajaram Mohan Roy Extn,

Sampangiramanagar, Bangalore – 560 027

Ph-080-40206309, 09916488864

Description of Study: In this research study, we will be comparing the effects of yoga versus relaxation technique and conventional antiemetic treatment on nausea and vomiting following moderately emetogenic chemotherapy administration in patients with solid tumours. In this study 120 subjects will be recruited. This study will be conducted at HCG BIO.

The objective of this study is to assess whether stress such as anxiety, depression perceived stress and changes in bowel motility enhance nausea and vomiting following chemotherapy and also evaluate if therapies like yoga and relaxation can reduce them. In this study all participants on chemotherapy will receive conventional antiemetic therapy as followed in the study. In addition one group will receive yoga program of 25 min duration, another group will receive relaxation technique of 25 min duration and the third group will be only on antiemetic during their chemotherapy. We are comparing yoga with relaxation as both are known to reduce stress. However we feel

yoga may also affect bowel movements and thereby reduce vomiting and nausea following chemotherapy administration.

You could be a participant based on your cancer diagnosis and because you are receiving chemotherapy. The total duration of study for each participant is 4 months or 5 cycles of chemotherapy. You will be taught yoga / relaxation intervention by a trained therapist before your first chemotherapy cycle and you will be asked to practice the same twice a day for next six days and once a day thereafter for next 3 cycles at home. You will be provided video/audio cassettes / CDs of the yoga and relaxation modules for home practice in the instructor's voice, you will be asked to maintain a daily log of practices and field personnel will ensure your compliance to practice at regular intervals by calling you or visiting you. If you agree to participate, you will be interviewed by the medical oncologist and study personnel and then asked to complete surveys to determine your mood, symptoms, level of depression and quality of life.

You will have a 50/50 chance (like flipping a coin) of being placed in one of three groups (randomized). Neither your doctor nor you will make the choice, so that bias in the study is reduced. The three groups are (a) the yoga Group + Antiemetics or (b) the relaxation Group + Antiemetics and c) Antiemetics only group.

You will undergo ECG testing and gastric motility testing at the study start and after seven days of intervention and again after 4 cycles of chemotherapy. This is a non-invasive procedure where electrode patches will be placed on your chest and abdomen and monitored for cardiac activity and bowel movements before and after drinking 30 ml of water. The procedure will take only 30 minutes of your time. In addition you have to fill self report questionnaires that will take another 30 minutes. You will have to spend about half an hour every day for yoga/relaxation practices for 3 months.

Risks/Benefits to the Participant: There are no significant risks involved with participation in this study. The information you will be asked to discuss will be

personal and will require you to reveal information about your mental wellbeing, moods and how you are coping with chemotherapy related nausea and vomiting. However you will only be asked to respond with a number or a single word and will not be asked to elaborate upon responses. You will also be asked to cooperate for recording ECG and EGG. This is a non-invasive procedure and will not cause any harm to you. The investigations pertaining to the study and yoga therapy charges will be free during this study. However the charges for chemotherapy medicines and antiemetic therapy will have to be borne by you. You will also have the opportunity to gain knowledge that might improve treatment options available to patients with cancer.

Yoga practices will be introduced in a gentle and slow pace to help you relax. These practices will have no religious connotation nor affect the religious sentimentality of any participant. These are simple practices and have been tested earlier in similar patients and have been found to be safe. If you have any concerns about the risks or benefits of participating in this study, you can contact Dr RaghavendraRao at the number provided in the first page.

In case of Injury to the subject:

If you are injured as a result of being in this study due to yoga postures or electric shock resulting from the ECG or EGG recording, you will be provided all the necessary treatment for injuries arising due to these circumstances. You should contact the study staff or report to the clinical supervisor in the event of such a claim.

Cost and Payments to the Participant: There is no cost for participation in this study. Participation is completely voluntary and no payment will be provided. Also, any patient requiring any other form of therapy, will be informed of the same and no cost

will be borne for these from our end. However such participants will be permitted to continue with the treatment program already commenced unless they wish otherwise.

Confidentiality: Information obtained in this study is strictly confidential unless disclosure is required by law. You will be assigned a research number, rather than your name, which will be recorded on the assessments done. All data will be secured in a locked filing cabinet. Your name will not be used in the reporting of information in publications or presentations. However they will be made available to other workers of the study/IEC and medical regulatory authorities.

Participant's Right to withdraw from the Study: You have the right to refuse to participate in this study, the right to withdraw from this study and the right to have your data destroyed at any point during or after the study, without penalty, except in situations that violate state and/or federal law and regulations. You will not lose any benefits to which you are otherwise entitled to.

Termination of Participation: Your participation in the study may be terminated by the Investigator under such circumstances wherein:

i) The subject fails to adhere to the requirement and regulations put forth in the study.

ii) The subjects default on the treatment or invention or investigations frequently.

iii) Intolerable side effects.

In case of any intentional/serious harm or injury or adverse event resulting from participation in the study, you may contact the Investigator Dr.Raghavendra. For your rights in the study you may contact the Institutional Ethics Committee SecrataryDr. Ganesh Naik at 9945010487.

Voluntary Consent by the Participant

Participation in this research project is completely voluntary and your consent is required before you can participate in this research. If significant new information related to this study becomes available and this information may affect your willingness to participate in this study, Dr.RaghavendraRao will alert you immediately.

Declaration by the Subject

I have read this consent form (or it has been read to me) and I fully understand the contents of this document and voluntarily consent to participate. All of my questions concerning this research have been answered in the language I understand. If I have any questions in the future about this study, they will be answered by the investigator mentioned above or his staff. I understand that this consent ends at the conclusion of this study.

Participant's Signature _____ Date: _____

Witness's Signature _____ Date: _____

Counter signed by:

Signature of the Investigator/designee Clinical Supervisor.

A copy of this form has been given to me

Signature: Participant/ LAR/Witness.

12th July 2008

Dr. Raghavendra Rao
Bangalore Institute of Oncology
Bangalore-560027.

Sub: CEC comments on CINV study

Protocol Title: Comparison of yoga vs. relaxation on chemotherapy induced nausea and vomiting (CINV) outcomes following chemotherapy.

Dear Dr. Raghavendra Rao,

The Central Ethics Committee of HCG held a meeting on 11th July 2008 at 5.00 p.m in Board Room of Old BIO. Following members were present in meeting:

1. Dr. K.S Gopinath – Member Secretary
2. Dr. Prof Sheshadri - Member (Acting Chairperson)
3. Justice Ashwath Narayan Rao - Member
4. Dr. Sudha Suresh – Member
5. Smt. T.N. Manjula Devi – Member
6. Dr. Ravi B Diwakar - Special invitee –Member SRC

The committee discussed the following documents related to the study:

1. Study Protocol Version No.2 dated 10th December 2003.
2. Informed Consent Form English
3. Informed Consent Form Kannada
4. CRF / Study questionnaires.

Dr Raghavendra Rao presented the study and the CEC members suggested to incorporate the suggestions recommended by SRC regarding inclusion /exclusion criteria such as exclusion of patients with liver metastases. The CEC recommends the study for approval

The committee decided to approve the above mentioned study in its present form to be conducted at Bangalore Institute of Oncology, Bangalore

HealthCare Global Enterprises Ltd.
HCG Towers, # 8, P. Kalinga Rao Road, Sampangiram Nagar, Bangalore : 560 027.
Tel / Fax : +91-80-4020 6000 www.hcgoncology.com

CENTRAL ETHICS COMMITTEE

Ethics Committee Membership List/Attendee List

Venue: Board Room, Bangalore Institute of Oncology (Old Building)
4th floor, 44-45, 2nd Cross Lalbagh Double Road,
Raja Ram Mohan Roy Extension, Bangalore – 560027.

CEC Meeting Date: 11th July 2008

Time: 5.00 p.m onwards

S. No	Name	Qualification	Designation	Conflict of Interest	Sign and Date
1.	Dr. Chandrashekar Shetty.S	M.S	**Chairman** (Ophthalmologist)		
2.	Justice Ashwath Narayan Rao	Advocate	**Member** (Lawyer)		11.7.08
3.	Prof. U.Seshadri	Professor of Surgery	**Member** (Clinician)		
4.	Dr. K.S.Gopinath	M.S.	**Member Secretary** (Surgical Oncologist)		
5.	Dr. Raghavendra Rao	PH.D	**Member** (Basic Medical Scientist)		
6.	Dr. Sudha Suresh	Associate Dean	**Member** (Lay Person)		
7.	Smt. T.N. Manjula Devi	Senior Advocate	**Member** (Legal Expert)		

Dr.K.S.Gopinath
(Member Secretary)
Central Ethics Committee

2. QUESTIONNAIRES FOR ASSESSMENT

NAUSEA DIARY

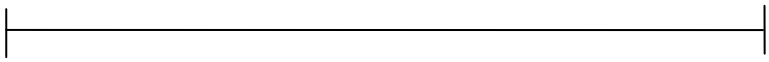
NAUSEA ASSESSMENT

Please rate your WORST level of nausea felt over the last 24 hours.

Date you completed this assessment:

Time you completed this assessment:

Indicate the worst level of nausea you have felt over the last 24 hours by drawing a vertical line (I) through the line below.



No Nausea

Nausea as bad as it could be

SEVERITY SCALE

Rate your severity of nausea using the descriptions provided below:

[1] ☐ None (No Nausea)

[2] ☐ Mild (uneasiness/ upset stomach that is manageable and minimally (if at all) affects daily activities.

[3] ☐ Moderate (increased uneasiness, sometimes with a feeling of having to vomit/throw up (but not vomiting), that has significant negative effect on the daily activities (for example, being unable to work, eat and drink, prepare food, care for children or others).

[4] ☐ Severe (Feeling sick and vomiting or feeling like you are going to vomit, and unable to perform most daily activities

Protocol identifier	Subject Identifier	Subject Diary	Visit Description Cycle ….. Day ….

EMETIC EPISODES

Did you have any vomiting and /or retching) within the previous 24 hours?

[y] ☐ Yes [N] ☐No

if no record the date and time of this assessment.

Rescue medication

Have you taken any medication for nausea or emesis (Vomiting/retching) within the previous 24 hours/

[y] ☐ Yes [N] ☐No

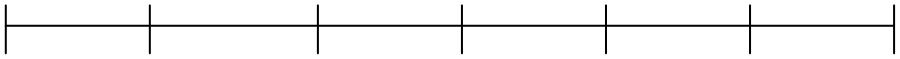
If yes , record the date, time and name of medication below

Date of rescue medication Day Month Year	Time of Rescue Medication Hr: Min	Name of Rescue Medication
Eg. 31 May 03	12:30	

Protocol Identifier	Subject Identifier	Subject Diary	Visit No: Cycle Day

FUNCTIONAL LIVING INDEX –EMESIS

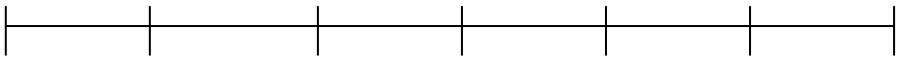
1. **How much of nausea you had in the past 5 days?**



1 2 3 4 5 6 7

None A great deal

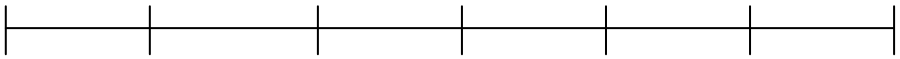
2. **Has Nausea affected your ability to maintain usual recreation or leisure activities in the past 5 days?**



1 2 3 4 5 6 7

Not at all A great deal

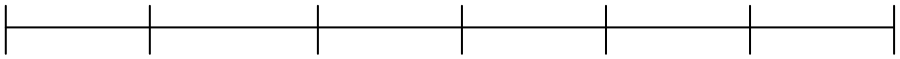
3. **How much has nausea affected your ability to make a meal or do minor household repairs during the past 5 days?**



1 2 3 4 5 6 7

A great deal Not at all

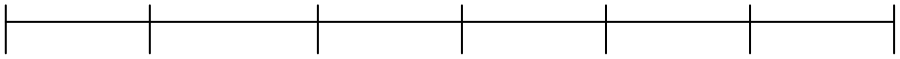
4. **How much has nausea affected your ability to enjoy a meal in the past 5 days?**



1 2 3 4 5 6 7

Not at all A great deal

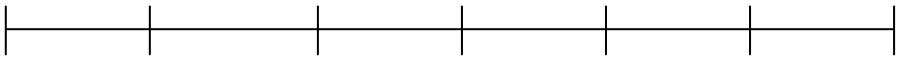
5. **How much has nausea affected your ability to enjoy drinking liquids in the past 5 days?**



1 2 3 4 5 6 7

Not at all A great deal

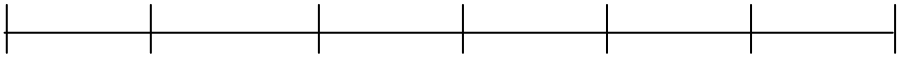
6. How much has nausea affected your willingness to see and spend time with family and friends, in the past 5 days?



1 2 3 4 5 6 7

A great deal Not at all

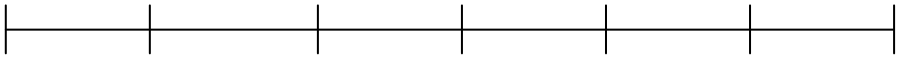
7. Has nausea affected your daily functioning in the past 5 days?



1 2 3 4 5 6 7

Not at all A great deal

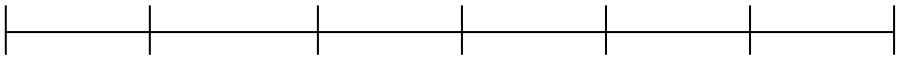
8. Rate the degree to which your nausea has imposed a hardship on you (personally) in the past 5 days.



1 2 3 4 5 6 7

Not at all A great deal

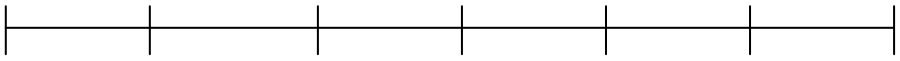
9. Rate the degree to which your nausea has imposed a hardship on those closest to you in the past 5 days.



1 2 3 4 5 6 7

Not at all A great deal

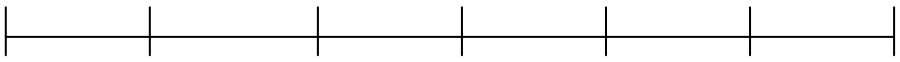
10. How much of vomiting you had in the past 5 days?



1 2 3 4 5 6 7

None A great deal

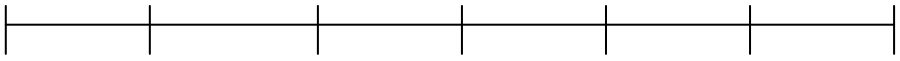
11. Has Vomiting affected your ability to maintain usual recreation or leisure activities in the past 5 days?



1 2 3 4 5 6 7

A great deal Not at all

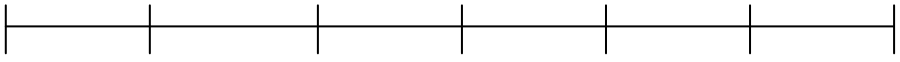
12. How much has Vomiting affected your ability to make a meal or do minor household repairs during the past 5 days?



1 2 3 4 5 6 7

Not at all A great deal

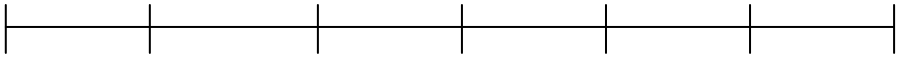
13. How much has Vomiting affected your ability to enjoy a meal in the past 5 days?



1 2 3 4 5 6 7

Not at all A great deal

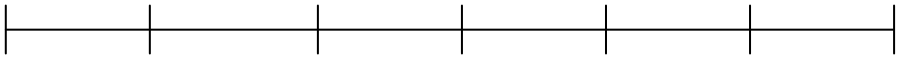
14. How much has Vomiting affected your ability to enjoy drinking liquids in the past 5 days?



1 2 3 4 5 6 7

Not at all A great deal

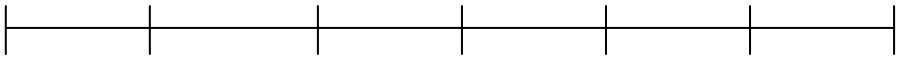
15. How much has Vomiting affected your willingness to see and spend time with family and friends, in the past 5 days?



1 2 3 4 5 6 7

A great deal Not at all

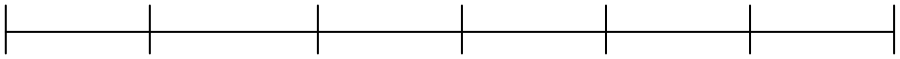
16. Has Vomiting affected your daily functioning in the past 5 days?



1 2 3 4 5 6 7

Not at all A great deal

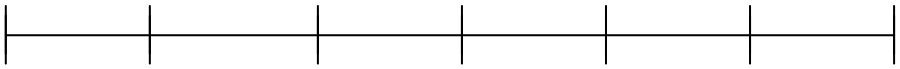
17. Rate the degree to which your Vomiting has imposed a hardship on you (personally) in the past 5 days.



1 2 3 4 5 6 7

Not at all A great deal

18. Rate the degree to which your Vomiting has imposed a hardship on those closest to you in the past 5 days.



1 2 3 4 5 6 7

A great deal Not at all

SPIELBERGERS STATE TRAIT ANXIETY INVENTORY (STAI)
SELF-EVALUTION QUESTIONNAIRE

STAI FORM X-1

Protocol No: Date:

Subject Identifier No: Visit No:

DIRECTIONS:A number of statements which people have used to describe themselves are given below. Read each statement and then tick in the appropriate number to the right of the statement to indicate how you feel at this moment. There is no right or wrong answers. Do not spend too much time on any one statement but give the answer, which seems to describe your present feelings best.

Choose the answers from the choice given below:

1. **NOT AT ALL.**
2. **SOMEWHAT.**
3. **MODERATELY SO.**
4. **VERY MUCH SO.**

1.	I feel calm	1	2	3	4	☐
2.	I feel secure	1	2	3	4	☐
3.	I am tense	1	2	3	4	☐
4.	I am regretful	1	2	3	4	☐
5.	I feel at ease	1	2	3	4	☐

6.	I feel upset	1 2 3 4	☐
7.	I am presently worrying over possible misfortunes.	1 2 3 4	☐
8.	I feel rested	1 2 3 4	☐
9.	I feel anxious	1 2 3 4	☐
10.	I feel comfortable	1 2 3 4	☐
11.	I feel self-confident	1 2 3 4	☐
12.	I feel nervous	1 2 3 4	☐
13.	I am jittery	1 2 3 4	☐
14.	I feel “high strung”	1 2 3 4	☐
15.	I am relaxed	1 2 3 4	☐
16.	I feel content	1 2 3 4	☐
17.	I am worried	1 2 3 4	☐
18.	I feel over-excited and “rattled”	1 2 3 4	☐
19.	I feel joyful	1 2 3 4	☐
20.	I feel pleasant	1 2 3 4	☐

HOSPITAL ANXIETY AND DEPRESSION SCALE

Protocol No: Date:

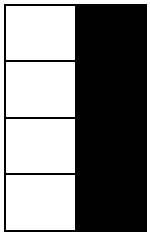
Subject Identifier No: Visit No:

Doctors are aware that emotions play an important part in most illnesses if your doctor knows about this feelings he will be able to help you more. This questionnaire is designed to help your doctor to know how you feel. Read each item and place a tick in the box opposite the reply which comes closest to how you have been feeling in the past week.

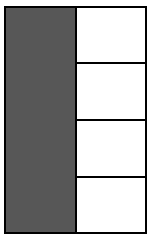
Don't take too long over your replies. Your immediate reaction to each item will probably be more accurate than a long thought of response.

Tick only one box in each section.

1. I feel tensed or wound up:
   Most of the time.
   A Lot of the time.
   Time to time, Occasionally
   Not at all.



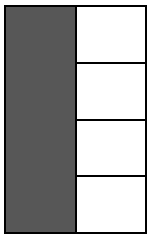
2. I still enjoy the things I used to enjoy:
   Definitely as much.
   Not quite so much.
   Only a little.
   Hardly at all.



3. I get a sort of frightened feelings as if some thing awful is about to happen:
   Very Definitely and quite badly.
   Yes but not too badly.
   A little but it does not worry me.

Not at all.

4. I can laugh and see funny side of things:



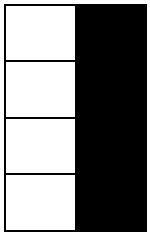
As much as I always could.

Not quite so much now.

Definitely not so much now.

Not at all.

5. Worrying thoughts go through my mind:



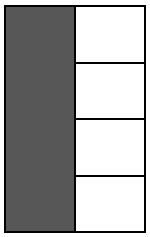
A great deal of the time.

A lot of the time.

From time to time but not too often.

Only occasionally.

6. I feel cheerful:



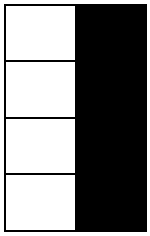
Not at all.

Not often.

Sometimes.

Most of the time.

7. I can sit at ease and feel relaxed:



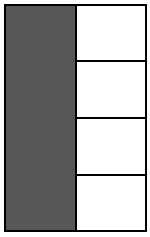
Definitely.

Usually.

Not often.

Not at all.

8. I feel as if I am slowed down.



Nearly all the time.

Very often.

Sometimes.

Not at all.

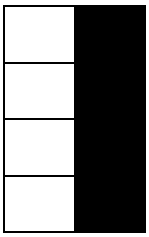
I get a sort of frightened feelings like ‘butterflies’ in the stomach.

Not at all.

Occasionally.

Quite often.

Very often.



9. I have lost interest in my appearance:

Definitely.

Quite a lot.

I may not take quite as much care.

I take just as much care as ever.

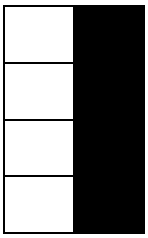
10. I feel restless as if I have to be on the move:

Very much indeed.

Quite a lot.

Not very much.

Not at all.



11. I look forward with enjoyment to things:

As much as ever I did.

Rather less than I used to.

Definitely less than I used to.

Hardly at all.

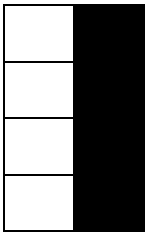
12. I get sudden feelings of panic:

Very often indeed.

Quite often.

Not very often.

Not at all.



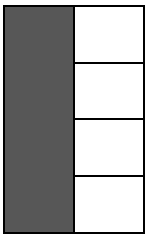
I can enjoy a good book or radio or TV Programme.

Often.

Sometimes.

Not often.

Very seldom.



PERCEIVED STRESS SCALE

Protocol No: ……. **Date:**

Subject Identifier No: …… **Visit No:**

Instructions: The questions in this scale ask you about your feelings and thoughts during the last month. In each case, please indicate with a check how often you felt or thought a certain way.

1. In the last month, how often have you been upset because of something that happened unexpectedly?

0	1	2	3	4
Never	Almost Never	Sometime	Fairly Often	Very Often

2. In the last month, how often have you felt that you were unable to control the important things in your life?

0	1	2	3	4
Never	Almost Never	Sometime	Fairly Often	Very Often

3. In the last month, how often have you felt nervous and "stressed"?

0	1	2	3	4
Never	Almost Never	Sometime	Fairly Often	Very Often

4. In the last month, how often have you felt confident about your ability to handle your personal problems?

0	1	2	3	4
Never	Almost Never	Sometime	Fairly Often	Very Often

5. In the last month, how often have you felt that things were going your way?

0	1	2	3	4
Never	Almost	Sometime	Fairly	Very

	Never		Often	Often

6. In the last month, how often have you found that you could not cope with all the things that you had to do?

0	1	2	3	4
Never	Almost Never	Sometime	Fairly Often	Very Often

7. In the last month, how often have you been able to control irritations in your life?

0	1	2	3	4
Never	Almost Never	Sometime	Fairly Often	Very Often

8. In the last month, how often have you felt that you were on top of things?

0	1	2	3	4
Never	Almost Never	Sometime	Fairly Often	Very Often

9. In the last month, how often have you been angered because of things that were outside of your control?

0	1	2	3	4
Never	Almost Never	Sometime	Fairly Often	Very Often

10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

0	1	2	3	4
Never	Almost Never	Sometime	Fairly Often	Very Often

Protocol No: ---------- Date: ----------

Subject Identifier No: ---------- Visit No: ----------

CHECKLIST FOR EVALUATING STATE OF AGNI WITH SPECIAL REFERENCE TO JĀṬARĀGNI - JIC

Symptom	0	1	2	3
1. Anorexia	none	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition, oral nutritional supplements indicated	Associated with significant weight loss or malnutrition, IV fluids, tube feeding or TPN indicated
2. Constipation	none	Occasional or intermittent symptoms, occasional use of stool softeners, laxatives, dietary modification or enema	Persistent symptoms with regular use of laxatives or enema indicated	Symptoms interfering with ADL, obstipation with manual evacuation indicated
3. Diarrhea	none	Increase of <4stools /day over baseline,	Increase of 4-6 stools/day over baseline, IV fluids indicated <24hrs,	Increase of _> 7 stools/day over baseline, incontinence, IV fluids _>24 hrs hospitalization,
4. Distension/ bloating, abdominal	none	Asymptomatic but evident on clinical examination	Symptomatic but not interfering with GI function	Symptomatic, interfering with GI function
5. Dry mouth	none	Symptomatic(dry or thick saliva)	Symptomatic and significant oral	Symptoms leading to inability to

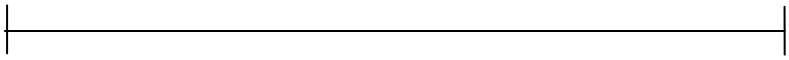
		without significant dietary alteration,	intake alteration,	adequately aliment orally, IV fluids, tube feedings or TPN indicated,
6. Flatulence	none	Asymptomatic but evident on clinical examination	Symptomatic but not interfering with GI function	Symptomatic, interfering with GI function ----
7. Heart burn/Dyspepsia	none	Asymptomatic but evident on clinical examination	Symptomatic but not interfering with GI function	Symptomatic, interfering with GI function
8. Taste alteration	none	Altered taste but no change in diet	Altered taste with change in diet, noxious or unpleasant taste, loss of taste.	----
9. Gastro-intestinal-others a) Heaviness of abdomen	none	Asymptomatic but evident on clinical examination	Symptomatic but not interfering with GI function	Symptomatic, interfering with GI function
b) Gurgling sound in the intestine	none	Asymptomatic but evident on clinical examination	Symptomatic but not interfering with GI function	Symptomatic, interfering with GI function
c) Eructations	none	Asymptomatic or very occasional	Symptomatic and frequent but not interfering with GI function	Symptomatic, interfering with GI function
d) Excessive salivation	none	Asymptomatic or very occasional	Symptomatic and frequent but not interfering with GI function	Symptomatic, interfering with GI function

Note: The symptoms mentioned as 9a, b, c, d categorized under gastrointestinal-others is graded depending on the patient's response (Subjective response)

Reference: The grading of symptoms mentioned in the above checklist is customized for this study based on Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 published by U.S. Department of health and human services, National Institutes of Health and National Cancer Institute

Visual analogue scale for assessing state of agni with special reference to Jāṭarāgni

1. Quantity taken at each meal (how much you are able to eat now than before)



Not able to eat at all Able to eat as much as earlier

3. RAW DATA

QUANTITY AT EACH MEAL												
SL.NO	CYCLE 1			C1-D5/D7			CYCLE 2			CYCLE 3		
	YOGA	JRT	WLC	YOGA	GRT	WLC	YOGA	JRT	WLC	YOGA	JRT	WLC
1	0	2	0	1	2		1	3		1	3	2
2	0	0	0	1	2	1	0		2	0	0	2
3	0	2	1	3	1	1	3	2	1	2	2	1
4	1	1	0		2	1	0	1	1	1	1	1
5	1	0	0	1	0	2	0	1	0	0	0	1
6	0	0	0	0	0	0	0	0	1	0	2	2
7	0		0	0	1	1	0	0	2	0	0	
8	0	1	0	0	1	1	0	1	2	1	0	0
9	0	0	0	1	2	1	2	1	1	1	3	1
10	1	3	0	1	3		0	0		1	3	
11	0	1	0	1	1	0	0	0	1	1	2	0
12		0	1	1	3	3	0	1	1	0	1	3
13	1	1	0	1	2	3		2	0		1	1
14	0	0	0	0	0	0	0	0	0	1	1	0
15	0	0	0	2	1	3	0	1	0	0	1	0
16		1	0	2	2	2	1	1	1	0	1	3
17	2	1	0	0	0	0	2	0	0	0	0	1
18	1	0	1	0	0	3	1	1	0	0	1	3
19	0	0	0	2	1	3	1	0	0	0	0	0
20	0	0	0	1	0	0	1	0	0	0	1	0
21	0	0	2		1	2		0	2		0	2
22	0	2	0	0	1	3	0	1	2	0	1	1
23	0	0	0	0	1	3	0	2	1	0	1	0
24	0	3	0		1		1	1	0	1	0	
25	2	1	2	1	1		1	1		1	1	
26	0	0	0	1	1	3		1	2		2	
27	0	0	0	0	1		1	0		0	1	
28	0	0	0	2	0		2	0		1	1	
29	1	0	0	2	0	0	2	0	0	0	2	0
30	0	0	0	2	0	0	1	0	0	2		2
31	0	0	0	2	1	0	0	1		1	0	

32	0		0	0	2	0	0	0	3	0	1	1
33	0	0	0	0	0	1	0	0	0	0	0	2
34	1	2	0	2	1	1	0	0	1	0	3	2
35	0	0	0	1	0	3	3	1	0	2	1	0
36	0	0	2	1	0	2	2	0		1		
37	0	0	3	2	3	0	1	0	2	1		1
38	0	0		2	3		0	1		0	0	
39	1	0		1	2		1	2		1		
40	0	0		3	2		1			3		
41	0	0		3	0			0				
42	0			0			0					

TOTAL AGNI												
SL NO.	Baseline			C1-D5/D7			CYCLE 2			CYCLE 3		
	YOGA	JRT	WLC	YOGA	JRT	WLC	YOGA	JRT	WLC	YOGA	JRT	WLC
1	1	7	2	6	11	0	6	18		8	16	9
2	3	0	6	12	19	15	6		10	1	9	9
3	0	11	2	8	13	6	7	5	5	9	5	1
4	5	2	0	0	11	4	2	3	2	6	10	2
5	3	3	0	2	5	6	1	3	2	1	1	4
6	7	6	3	2	7	2	2	2	5	2	8	8
7	0	1	1	1	4	14	0	0	6	2	0	0
8	0	4	0	5	9	9	0	4	7	2	1	3
9	1	0	0	5	16	4	5	4	9	9	4	7
10	1	9	0	11	13	0	1	5	0	6	5	
11	11	2	0	8	4	8	1	1	3	4	4	4
12	2	3	7	13	12	18	5	10	9	10	10	6
13	2	1	2	8	5	16		5	1		7	5
14	1	2	1	5	0	1	1	0	0	13	3	1
15	2	2	2	15	19	11	2	9	1	0	13	2
16	6	3	2	8	9	9	3	4	4	6	6	11
17	6	4	0	3	0	1	2	2	2	2	5	2
18	3	2	1	5	2	8	3	1	3	1	3	9
19	0	0	0	2	3	5	1	0	1	0	7	2
20	4	0	1	13	3	3	4	1	3	7	5	0
21	0	1	11	0	4	6		1	5		0	11
22	0	7	2	0	11	6	0	14	11	6	10	6
23	3	0	2	3	5	10	1	21	1	2	4	0
24	2	12	0	0	12	0	1	8	6	1	4	
25	3	3	9	11	5	0	5	6		5	2	
26	1	2	0	12	8	22		3	11		17	
27	3	1	4	2	3	0	5	1	0	0	8	0
28	0	0	0	8	0	0	5	0		4	5	
29	4	0	0	7	2	0	6	2	0	3	9	0
30	0	0	1	13	3	0	6	0	0	8		11
31	0	1	0	9	4	0	0	2		4	3	
32	0	0	0	6	9	5	5	0	13	0	2	3

33	7	0	3	0	0	6	3	0	5	1	0	11
34	8	9	0	15	8	1	0	3	1	0	11	5
35	0	0	2	1	0	11	3	2	2	2	2	1
36	0	0	2	4	0	2	5	0		3		
37	0	0	10	4	4	0	1	1	5	2		3
38	1	0		10	23		0	3		2	2	
39	9	0		4	9		1	3		9		
40	1	2		14	9		8			12		
41	1	0		10	0			0				
42	0			0			0					

BL-Baseline before intervention, C1 D7-After intervention (7 days post 1st chemo) C2-After intervention (post 2st chemo),C3-After intervention (post 3st chemo)

4. LIST OF TABLES

5. LIST OF FIGURES

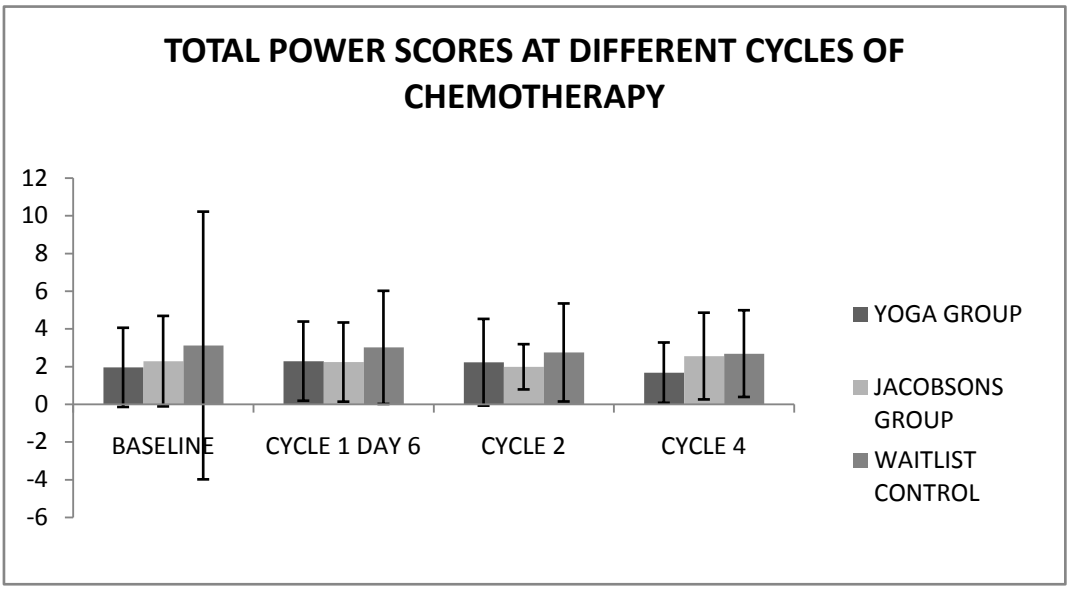
6. HRV RESULTS

Total Power: There was no significant change in total power either between groups or within groups.

Table A6.1: Comparison of Total power (TP) between Yoga, Jacobson's and Control (Waitlist) group using Non parametric independent sample Mann-Whitney test.

GROUP	TP (ms^2)			
	BASELINE	**CYCLE 1 DAY 6**	**CYCLE 2**	**CYCLE 4**
Yoga group Mean ± SD (N=39)	901.30 ± 972.6	999.34 ± 1.3	1782.83 ± 3.5	721.16 ± 1.1
Jacobson's group Mean ± SD (N=36)	990.11 ± 1.0	741.80 ± 609.0	756.26 ± 752.4	606.87 ± 580.8
Control group Mean ± SD (N=30)	1269.11 ± 1.6	549.93 ± 702.5	647.39 ± 786.9	569.96 ± 855.7
*p<0.05, **p<0.01, ***p<0.001 for within group effects **Conclusion: No Significant change in any group.**				

Fig. :A6.1 : Total power scores at different cycles of chemotherapy



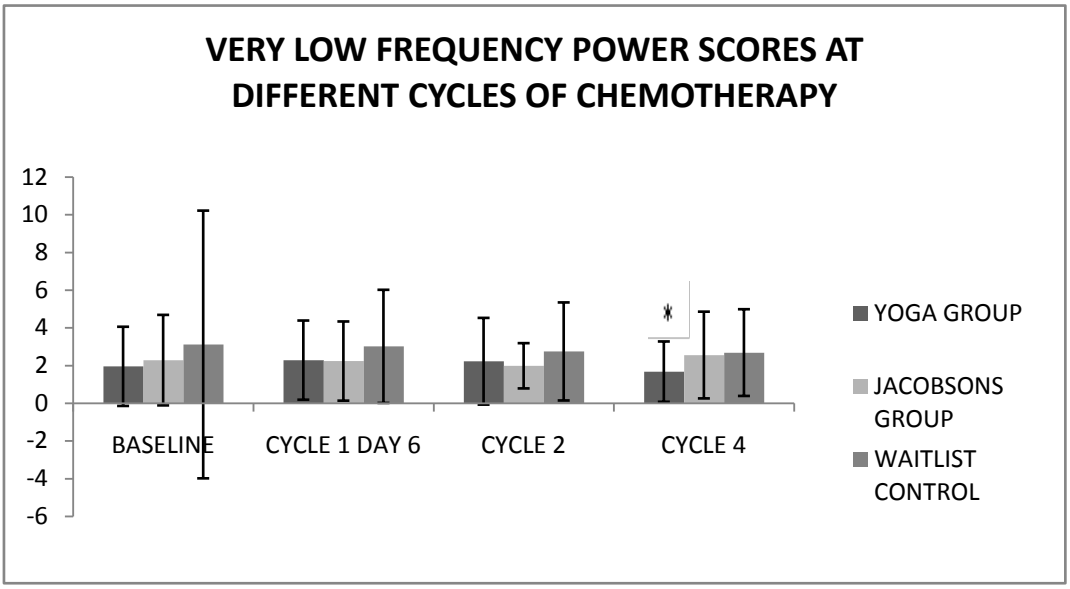
No Significance

Very low frequency power: there was a significant decrease in very low frequency power in yoga group after 3rd cycle of chemotherapy compared to baseline (z =-2.35, p=0.02) on Wilcoxons Sign Rank test. However there were no significant differences between groups.

Table A6.2: Comparison of Very low frequency power between Yoga, Jacobson's and Control (Waitlist) group using Non parametric independent sample Mann-Whitney test.

GROUP	VLFP (ms^2)			
	BASELINE	**CYCLE 1 DAY 6**	**CYCLE 2**	**CYCLE 4**
Yoga group(N=39) Mean ± SD	350.51 ± 364.0	353.01 ± 483.9	727.84 ± 1.4	253.69 ± 358.5*****
Jacobson's group(N=36) Mean ± SD	407.02 ± 344.7	338.55 ± 253.6	353.21 ± 277.0	303.27 ± 259.4
Control group(N=30) Mean ± SD	452.06 ± 609.5	221.45 ± 244.6	373.51 ± 610.6	340.60 ± 582.1
*p<0.05, **p<0.01, ***p<0.001 for within group effects **Conclusion: Significant decrease in yoga group in VLFP**				

Fig. : A6.2: Very low frequency power scores at different cycles of chemotherapy



* Within group effects Significant decrease in yoga group in very low frequency power in yoga group after 3rd cycle of chemotherapy

Low frequency power: There was significant decrease in low frequency power in yoga group after 3rd cycle of chemotherapy compared to baseline (z=-2.22, p=0.03) and at 2nd cycle of chemotherapy in control group compared to baseline (z=-2.21`, p=0.03). However there was no significant difference between groups. There was trend for increase in LF power in yoga whereas there was a trend for decrease in LF power in Jacobson's and control group.

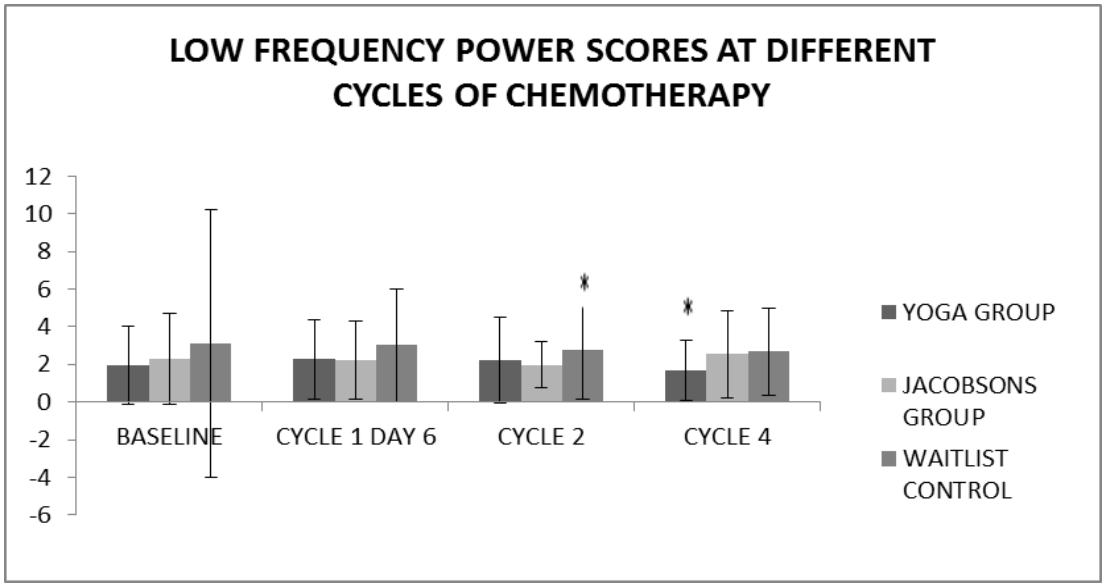
Table A6.3: Comparison of Low frequency power between Yoga, Jacobson's and Control (Waitlist) group using Non parametric Mann-Whitney test.

GROUP	LFP (ms^2)			
	BASELINE	CYCLE 1 DAY 6	CYCLE 2	CYCLE 4
Yoga group(N=39) Mean ± SD	210.81 ± 236.9	384.14 ± 604.8	402.94 ± 670.1	216.44 ± 424.3*
Jacobson's group(N=36) Mean ± SD	283.71 ± 503.8	219.69 ± 256.1	238.19 ± 397.3	131.77 ± 113.2
Control group(N=30) Mean ± SD	243.86 ± 388.9	164.28 ± 232.3	116.84 ± 124.5*	105.56 ± 122.9

*p<0.05, **p<0.01, ***p<0.001 for within group effects

Conclusion: Significant decrease in yoga group in low frequency power.

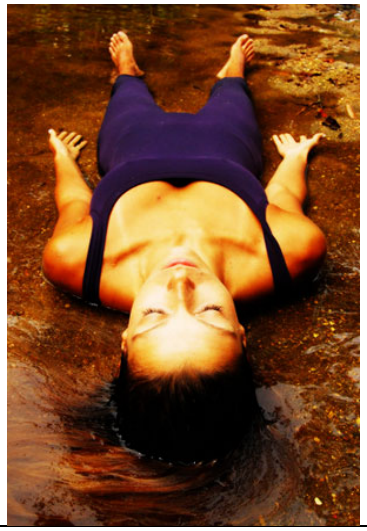
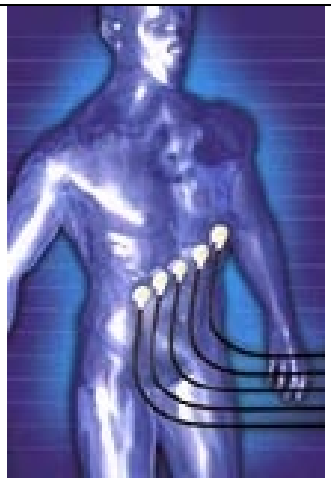
Fig.: A6.3 : Low Frequency Power Scores at Different Cycles of Chemotherapy



* Within group effects

Conclusion: Significant decrease in yoga group in low frequency power.

7. PLATES

	**1. Quick relaxation technique**
2. Tensing of group of muscles During Progressive muscle relaxation Technique	
	**3. Electro gastro gram leads (non-invasive procedure) applied on patients (in supine position) to capture the EGG (electrogastogram).**