"A COMPARATIVE STUDY OF TRANEXAMIC ACID MICROINJECTIONS VERSUS ND YAG LASER IN THE TREATMENT OF MELASMA"

By

DR. AMULYA Y S, M.B.B.S.

DISSERTATION SUBMITTED TO

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA,

IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF

DOCTOR OF MEDICINE (M.D.)

IN

DERMATOLOGY, VENEREOLOGY AND LEPROSY

Under the Guidance Of

Dr. RAJASHEKAR. T. S. M.B.B.S., M.D.

Professor & Head Of Department

DEPARTMENT OF DERMATOLOGY, VENEREOLOGY AND LEPROSY

SRI DEVARAJ URS MEDICAL COLLEGE, TAMAKA, KOLAR, KARNATAKA - 563101

APRIL-2021

SRI DEVRAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"A COMPARATIVE STUDY OF TRANEXAMIC ACID MICROINJECTIONS VERSUS ND YAG LASER IN THE TREATMENT OF MELASMA"** is a bonafide and genuine research work carried out by me under the direct guidance of **DR. RAJASHEKAR. T.S**, Professor and Head of the Department of Dermatology, Venereology and Leprosy, Sri Devaraj Urs Medical College, Tamaka, Kolar, in partial fulfillment of the requirement for the degree of **M.D. IN DERMATOLOGY, VENEREOLOGY AND LEPROSY**.

Date: Signature of candidate

Place: Kolar **Dr.AMULYA Y S**

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA.

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"A COMPARATIVE STUDY OF TRANEXAMIC ACID MICROINJECTIONS VERSUS ND YAG LASER IN THE TREATMENT OF MELASMA"** is a bonafide and genuine research work done by **DR.AMULYA Y S** in partial fulfillment of the requirement for the degree of **M.D IN DERMATOLOGY, VENEREOLOGY AND LEPROSY** as per regulations of SRI DEVRAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, KOLAR.

Date:
Place: Kolar

Signature of Guide
DR. RAJASHEKAR.T. S **MD.**
Professor and Head,
Department Of Dermatology,
Venereology and Leprosy,
Sri Devaraj Urs Medical College.
Tamaka, Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION RESEARCH, TAMAKA, KOLAR, KARNATAKA.

ENDORSEMENT BY THE HOD, PRINCIPAL/HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"A COMPARATIVE STUDY OF TRANEXAMIC ACID MICROINJECTIONS VERSUS ND YAG LASER IN THE TREATMENT OF MELASMA"** is a bonafide and genuine research work done by **DR. AMULYA Y S** under the guidance of **DR. RAJASHEKAR.T. S**, Professor and Head of Department of Dermatology, Venereology and Leprosy, Sri Devaraj Urs Medical College, Tamaka, Kolar.

Signature of HOD
DR. RAJASHEKAR. T.S
Professor & Head,
Department of Dermatology
Sri DevarajUrs Medical College,
Tamaka, Kolar
Date:

Place: Kolar

Signature of Principal
DR. P.N.SREERAMULU
Principal,
Sri DevarajUrs Medical College,
Tamaka, Kolar
Date:
Place: Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH, TAMAKA, KOLAR, KARNATAKA

ETHICAL COMMITTEE CERTIFICATE

This is to certify that the ethics committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved the dissertation work of **DR.AMULYA Y S**, a postgraduate student in the Department of Dermatology, Venereology and Leprosy of Sri Devaraj Urs Medical College entitled **"A COMPARATIVE STUDY OF TRANEXAMIC ACID MICROINJECTIONS VERSUS ND YAG LASER IN THE TREATMENT OF MELASMA"** to be submitted to **SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA KOLAR.**

Signature of Member Secretary
Ethical committee.
Date:

Signature of Principal
Dr.P.N SREERAMULU
Sri Devaraj Urs Medical College,
Tamaka, Kolar

Place:Kolar

Kolar, Karnataka.

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

COPY RIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that the Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar, Karnataka shall have the rights to preserve, use and disseminate this dissertation/thesis in print or electronic format for academic /research purpose.

Date:

Place: Kolar

Signature of the candidate

Dr AMULYA Y S

Sri Devaraj Urs Academy of Higher Education and Research

Certificate of Plagiarism Check for Dissertation

Author Name	Dr AMULYA Y S
Course of Study	MD DERMATOLOGY
Name of Major Supervisor	Dr. Rajashekar T.S
Department	Dermatology
Acceptable Maximum Limit	10%
Submitted By	librarian@sduu.ac.in
Paper Title	A COMPARATIVE STUDY OF TRANEXAMIC ACID MICROINJECTIONS VERSUS ND YAG LASER IN THE TREATMENT OF MELASMA
Similarity	7%
Paper ID	178863
Submission Date	2020-11-07 11:34:04

Signature of Student

Signature of Major Advisor

Head of the Department

University Librarian

Director Of Post Graduate Studies

* This report has been generated by DrillBit Anti-Plagiarism Software

ACKNOWLEDGEMENT

One of the joys of completion of this dissertation is to look over the journey past and remember and thank all the people who have helped and supported me along this long but fulfilling road. First and foremost, I thank the Almighty for giving me the strength and ability to carry out this study.

I am deeply indebted and grateful to my guide, ***Dr.Rajashekar. T.S.*** *Professor and Head, Department of Dermatology, Venereology and Leprosy, Sri DevarajUrs Medical College, for his able guidance, support, timely advice and constant encouragement throughout the period of the study.*

I am very grateful to ***Dr Hanumanthayya K****, Professor, Department of Dermatology, Venereology and Leprosy, Sri DevarajUrs Medical College, for his guidance and support.*

I thank ***Dr. Suresh Kumar K****, Assistant Professor, Department of Dermatology, Venereology and Leprosy, Sri DevarajUrs Medical College, for his advice and support during my post graduation.*

I would also like to warmly extend my gratitude to ***Dr.Uday Kumar S, Dr SnehaKrishnoji Rao****, Senior Residents, Department of Dermatology, Venereology and Leprosy, Sri Devaraj Urs Medical College, for their constant encouragement.*

No words can express the gratitude I feel towards my beloved parents, ***Mr.Sathyanarayana Prasad*** *and* ***Dr Anuradha G****, whose countless sacrifices and endless love has made me who I am today in life.*

I also thank my brother, ***Dr Chaitanya Y S*** *for his motivation and for being a constant source of strength.*

I thank my husband, ***Dr Sajay Reddy****, for his unending love and support, and also being an inspiration to aim higher*

*I am thankful to my postgraduate colleague, **Dr. GVL Naveena**, my seniors and dear juniors for all their love, motivation and help.*

I am truly blessed in having the most wonderful friends and would like to thank them for their endless support.

I will be failing my duty if I do not thank all my patients involved in this study, without whose co-operation and patience this study would have been impossible.

*Last, but not the least, I would like to express my gratitude to the **Almighty** for all his blessings.*

Date: Signature of candidate

Place: **Dr.Amulya Y S**

LIST OF ABBREVIATIONS

SL NO	ABBREVATIONS	FULL FORMS
1	AA	Arachidonic acid
2	ACTH	Adrenocorticotrophic
3	ADR	Adverse Drug Reactions
4	AHA	Alpha Hydroxy Acids
5	bFGF	Basic fibroblast growth factor
6	DAG	Diacylglycerol
7	DGAR	Diglyceride acyl transferase
8	DOPA	3,4-dihydroxyphenylalanine
9	ER	Estrogen receptor
10	ET-1	Endothelin-1
11	FA	Fluocinolone Acetonide
12	FABP4	Fatty acid binding protein 4
13	FSH	Follicle stimulating hormone
14	GA	Glycolic Acid
15	INOS	Inducible nitric oxide synthase
16	HRT	Hormone replacement therapy
17	HQ	Hydroquinone
18	KA	Kojic Acid
19	KLK16	Human kallikrein16
20	LH	Leuteinizing hormone

21	LPL	Lipoprotein lipase
22	MASI	Melasma Area and Severity Index
23	MITF	Microphthalmia Associated Transcription Factor
24	mMASI	Modified Melasma Area and Severity Index
25	MSI	Melasma Severity Index
26	MSH	Melanocyte Stimulating Hormone
27	Nd:YAG	Neodymium-doped yttrium aluminium garnet
28	NHERF	Sodium -hydrogen exchanger regulatory factor
29	NMDA	N-methyl-D-aspartate
30	NFGR	Nerve Fibre Growth factor
31	NO	Nitrous oxide
32	OCP	Oral Contraceptive Pills
33	PIH	Post Inflammatory Hyperpigmentation
34	PPAR-α	Peroxisome proliferator-activated receptor-alpha
35	PPD	Persistent Pigment Darkening
36	PDL	Pulsed Dye Laser
37	POMC	Pro –piomelanocortin
38	RA	Retinoic acid
39	RAR	Retinoic Acid Receptor
40	RCM	Reflectance Confocal Microscopy
41	ROS	Reactive Oxygen Species

42	RT-PCR	Reverse transcription polymerase chain reaction
43	Sc-uPA	Single chain urokinase Plasminogen activator
44	SCF	Stem Cell Factor
45	SD	Standard Deviation
46	SPF	Sun Protection Factor
47	SPRR	Small proline rich protein
48	TCA	Trichloroacetic Acid
49	TXA,TA	Tranexamic acid
50	TYR	Tyrosinase
51	TYRP	Tyrosinase Related Protein
52	UVR	Ultraviolet radiation
53	VEGF	Vascular Endothelial Growth Factor
54	Wnt	Wingless-related integration site
55	WIF-1	Wntinhibitoryfactor-1

ABSTRACT

INTRODUCTION

Melasma is a hyperpigmentation disorder particularly affecting face, associated with significant psychological impact and the treatment should make an effective change to make patient satisfaction. The management of melasma is challenging and requires a long-term treatment plan along with avoidance of triggering factors. This study is aimed at assessing the efficacy of tranexamic acid microinjections versus Nd YAG laser in treatment of melasma

MATERIALS AND METHODS

The study was double blinded randomized trial among 64 subjects; 32 in tranexamic acid microinjections (GroupA) and 32 in the Nd YAG laser group (Group B). Patients with facial melasma belonging to both sexes, within an age group of 18 -50 years, and willing to undergo treatment and follow up were included in the study. Patients who were on other melasma therapies within last 6 months and having unrealistic expectation from the treatment were excluded from the study. Group A patients received intralesional Tranexemic acid and Group B patients received Nd YAG laser .Evaluation of the patients was done by detailed history, clinical examination and Melasma Area and Severity Index (MASI) score at baseline, 2 nd week and 4th week. Also side effects and recurrence were also assessed during the time. The data was entered in Microsoft excel sheet and a master chart was prepared and it was analysed using IBM SPSS software version20.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Inferential statistics was done using appropriate tests. P value <0.05 was considered statistically significant.

RESULTS

The mean (SD) age in years of the Tranexamic acid group and Nd YAG laser group was 39.25(8.41) years and 37.2(8.64) years respectively .In our study majority 38(59.4%) of the study subjects were females. The study showed that in both the groups malar type of melasma was present mostly 19(59.4%) and 20(62.5%)].The two weeks score mean (SD) for the Tranexemic acid and Nd YAG laser group was 14.75(4.63) and 14.88(5.70) respectively. The four weeks score mean (SD) for the tranexamic acid group and Nd YAG laser was 13.28(4.68) and 10.81(4.68) respectively which was statistically significant.

CONCLUSION

The study showed that both intralesional Tranexemic acid and Nd YAG laser were helpful in the treatment of melasma .But Nd YAG laser has an effective role in treating melasma along with other modalities

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF GRAPHS

INTRODUCTION

INTRODUCTION

Pigmentation which is acquired is the most distressing condition particularly if it affects the face[1] .There are many types of facial pigmentation types where melasma is a commoner one. Melasma is an acquired hypermelanosis of the face manifesting as light brown to dark, muddy brown macules on the face. People with Fitzpatrick skin photo types III- V, existing in regions of powerful ultraviolet (UV) light exposure are more usually affected [2]. Melasma affects the self-esteem of the patients [3]. Management is hard, often unacceptable and sustained treatment is required to maintain the results as reversions are inevitable[4] .

Appropriate patient counselling, sufficient sun protective actions and topical depigmenting agents (interfering with melanin synthesis) include the primary line of treatment. Different topical agents functions on various steps of melanogenesis thus proving to be an apt reason for combining them for the treatment.[5]Though common in both sexes, melasma is more common in females. The treatment of melasma has always been challenging and various modalities of treatment include broad spectrum sunscreens, hydroquinone with various concentration, tretinoin, fluorinated steroids, salicylic acid, glycolic acid, azelaic acid kojic acid, lactic acid, chemical peels, laser therapy like Q-switched ruby, Alexandrite, Nd:YAG laser etc.

Cosmetics also assume an important role in the management of this

condition is a temporary means of camouflage.

This study aimed at comparing the effectiveness of intralesional tranexamic acid and Nd YAG Laser in the treatment of melasma

AIMS & OBJECTIVES

OBJECTIVES

Aims and Objectives of the Study:

1) To assess the efficacy of Tranexamic acid in the treatment of melasma.
2) To assess the efficacy of Nd YAG laser in the treatment of melasma.
3) To compare the therapeutic effectiveness of Nd YAG laser with Tranexamic acid microinjections in melasma.

REVIEW OF LITERATURE

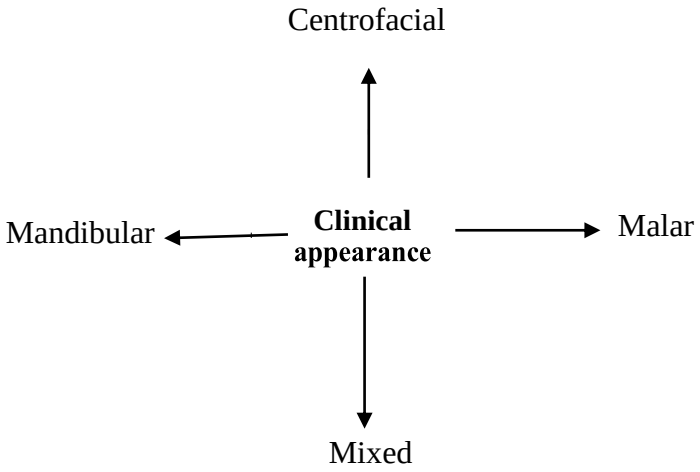
REVIEW OF LITERATURE

Melasma and its classification

Melasma is a chronic, recurring and acquired facial melanosis seen as symmetrical, hyperpigmented light to dark brown or greyish brown patches usually seen over the sun exposed areas mainly the face. The pigmentation can be like a constellation of macules, linear or large patches. Melasma is basically a dysfunction in human melanogenesis[5]

There are different classification types of melasma based on distribution, histology, duration and recurrence, diagnosis and site of appearance

Table 1: Classification based on distribution and clinical appearance [2]



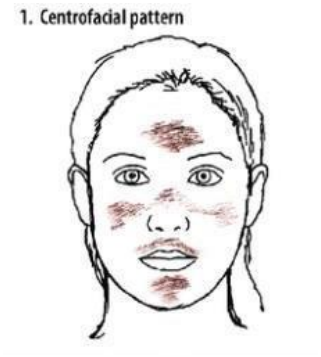
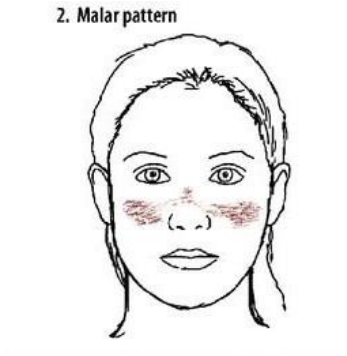
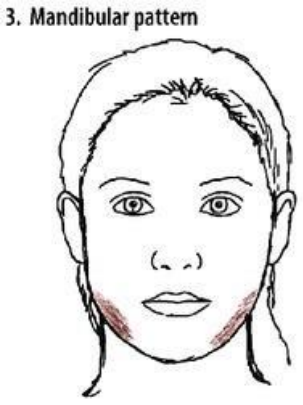
1	 CENTROFACIAL PATTERN	Seen in 63% of patients Most common pattern Involvement of cheeks, forehead, nose, upper lip &chin
2	 MALAR PATTERN	• Seen in 21 % of the patients • Distributed over the cheeks alone or cheeks and nose
3	 MANDIBULAR PATTERN	Seen in 16% of the patients Seen along ramus of the mandible
4	MIXED PATTERN	More than one pattern coexisting in the same patient

Table 2: Classification based on histology and Wood' slamp [6]

Type	Normal light	Wood's light	Histology	Response to treatment
Epidermal	Light brown	Enhancement of contrast	Melanin deposition in basal and suprabasal layers of epidermis	Good
Dermal	Bluish grey	No enhancement	Melanin laden melanophages seen in superficial and mid dermis	Poor
Mixed	Dark Brown	Some areas show contrast enhancement	Melanin deposition found in epidermis and dermis	Partial
Indeterminate	Bluish grey	Not evident	Melanin deposition in the dermis	Unpredictable

Table 3: Based on dermoscopy and Reflectance confocal microscopy(RCM)[7,8]

Diagnosis of melisma can be done by Dermascopy. Lesions of melasma demonstrate disperse reticular pigmentation in a variety of shades of brown without affecting follicular openings.

Types	Dermoscopy	RCM
Epidermal melasma	If confined to stratum corneum- dark brown colour and well defined border Not involve follicular openings If involving lower layers of epidermis- appear light brown with irregular network	Hyper refractile cobblestone cells and dendritic cells
Dermal melasma	Blue or bluish grey with pseudo reticular pigmentation	Plump bright cells, ragged and less refractile lacy structures. Dark round to tubular structures.

Based on duration of disease

- Transient: Usually persists for one year and disappear after the stimuli ceases to occur like hormones
- Persistent: This type will remain even after the triggering factor is removed. This can be due to the presence of other overlying triggering factors which still make the melasma last.

Based on the site

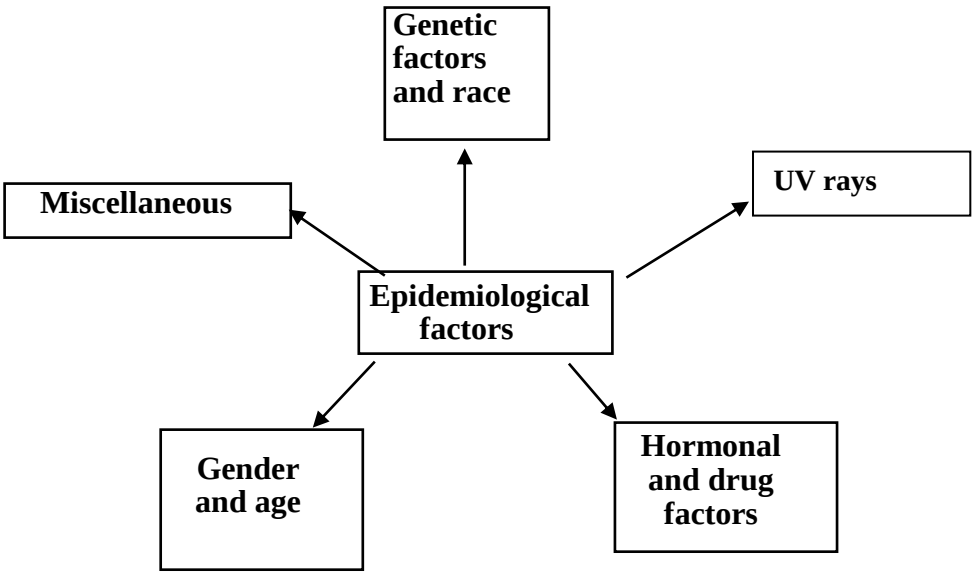
- Facial-forehead, cheeks, chin, nose and mandible
- Extra facial: areas of neck, sterna areas, forearm and back

Epidemiology of melasma Prevalence

A variety of epidemiologic studies measured the occurrence of melasma in the common inhabitants at 1% and in high risk inhabitants at 9 –50% [9-12]. A prospective study done in Latino females in the south western United States noted occurrence of 8.8%[10]. Another longitudinal study on melasma prevalence in a New York City found a prevalence of 8.2% among 1000 Latino subjects [9]. A study of 3298 citizens in Saudi Arabia exposed 2.9% occurrence, in comparison to 13.4 –15.5% seen in an Arab- American population in Michigan [13,14]. In addition, a retrospective study in a health center in Ethiopia established 1.5% prevalence [15]. A study done in Nepal in the year 2008 with 546 patients, melisma was ranked to be the 4th common pigmentary disorder[16]. Sarkar et al. in a study done in tertiary care hospital of New Delhi noted a prevalence of melasma to be about 20.5% in men [3]

.

Predisposing factors of melasma and its pathogenesis



Gender and age

The most significant association is between melasma and gender. All studies showed a rising percentage of women being affected by melisma dissimilar to men. Studies show that the disease is 7 - to 9-times fold more often in women than men[17]. Only 5 -10 % is seen in males. In a multi center study done on 953 melasma subjects in Brazil established a 39:1 ratio [18]. An Indian study showed 4: 1 women to men ratio [19]. The reason can be due to the difference in physiological and hormonal effects between the both genders.

There is a significant association present amid melasma and the age of commencement. Some studies state that 60% of the patients build up melasma under 30 years of age [20]. Other study done in brazilian patients stated extra -facial melasma being more frequent in menopausal women [21].

Genetic factor and Race

Family history has a significant association in melasma. 55– 64% of subjects with melasma have affirmative family history was observed in several studies [12, 22]. Genes accountable are concerned in pigmentary, inflammatory, hormonal and vascular reactions.

Subjects with Fitzpatrick skin type II and III a have fewer possibility to have a positive family history than in subjects with darker skin types (IV–VI) [21, 23] It is theorized that the type I rarely causes increase in pigmentation whereas the type VI is already pigmented to the maximum. Hence type I and type VI skin types are with stable pigmentation. This is also supported by the low incidence of melasma in fair skin type that is the Europeans and the people with type VI skin type – the Negros. For melasma delayed tanning is more important than burning [24].

In a study done on 2,000 skin subjects of black origin in Washington, DC, exposed 3rd frequently seen skin disease were pigmentary troubles other than vitiligo [25]. Of these patients, the preponderance had a diagnosis of post inflammatory hyperpigmentation, followed in frequency by melasma. However, epidemiological studies have described elevated occurrence in extra pigmented phenotypes, such as East Asians (Japanese, Korean and Chinese), Indian, Pakistani, Middle Eastern and Mediterranean - African. It is frequent amongst Hispanic-Americans and Brazilians who reside in intertropical areas, where there is larger coverage to ultraviolet radiation (UVR) [9, 26].

Certain races relatively showed a higher genetic predisposition. The prevalence was observe d to be 10 to 70% in studies from Iran, Singapore and in Latino men. Affirmative family history has been stated in 40% women subjects and 20% men subjects of melasma in a study from southeast Asia[27].

Outcome of a transcriptional investigation study executed in lesional samples in comparison with regular skin discovered that many melanogenesis-related genes and melanocyte markers such as TYR, MITF, SILV and TYRP1152 were up regulated. A subset of wnt pathway modulator genes (wnt inhibitory factor 1, produced frizzled related protein II and wnt5a 0) were observed to be differentially manifested in lesional skin[28].

Genes related to lipid metabolism :

PPARα, ADIPOQ, FABP4, perilipin1(PLIN1) and lipoprotein lipase (LPL),DGAT2L3 and PPARGC1A were observed to be decreased in the melasma lesional skin[29].

Genes involved with skin barrier function:

Current studies have Reported that melasma skin is having features of impaired integrity of stratum corneum and slowing of barrier revival found onstage Of TEWL noted by tape stripping done on melasma lesions.. Chung et al. have revealed alteration in degree of the appearance of genes that are directly or not directly concerned in skin barrier

function,i.e.S100AB.SPRR2A,SPRR2B and KLK16 are decreased by >2fold in lesional skin in comparison with surrounding skin [30].

Gene level expression by means of estrogens:

PDZ domain protein kidney1 (PDZK1) gene,whose expression is up regulated by oestrogens, has been observed to be upregulated in melasma lesional skin. PDZK1 is an affiliate of sodium-hydrogen exchanger regulatory factor (NHERF) family proteins, therein melanocytes and keratinocytes and enhances melanogenesis and melanosomes transport via ERs [31].

Gene expression studies on lesional skin observed an increase in estrogen sulfotransferase 1E, member concerned in estrogen metabolism. Chung et al. in in their study on gene expression profiling in Korean women showed genes concerned in the activity of testosterone 17 -β-dehydrogenase like hydroxyl steroid(17 -β) and dehydro genase 2(HSD17B2)and aldo- keto reductase family 1, member c3(3 -α-hydroxy steroid dehydrogenase, type 2)(AKR1C3) i n lesional skin were found to be upregulated [30].

Non coding RNA also appear to contribute in the pathogenesis of Melasma in a current melanocyte-keratinocyte culturestudy,theH19 gene which transcribes a noncoding RNA was established to be considerably down-regulated in lesional skin[31]. Stimulus of melanogenesis and transport of melanin to keratinocytes were linked with reduced transcription of H19

suggesting the role of this gene in evolution of melasma[31].

Other genes: Activation of INOS(inducible nitric oxide synthase) in Keratinocytes on UV exposure contributing to the melanogenesis process has also been suggested in melasma, seemingly due to activation of AKT/ nuclear factor kappa B pathway [32]. Genes stating guanine mediators like guainine deaminase and INH has been observed to be elevated in melasma lesional skin. NQO1 is a vital enzymatic antioxidant that has been observed to augment melanin synthesis, probably intervening the repression of tyrosine degradation and this has been observed to be upregulated in one study[33].

Hormonal and drug factors

Melasma is commonly seen when the female sex hormones are at a rise or at most demand. Estrogen and progestins are also found to be involved in development of melasma. Pregnancy, oral contraceptives and HRT are the common activating factors. A study in 1967 among women who developed melasma was taking oral contraceptives. 87% reported to have it at the time of pregnancy [34]. In third trimester of pregnancy , there is stimulus for melanogenesis, and the augmented stage of placental, ovarian and pituitary hormones provide justification that melasma linked with pregnancy. Alteration of melanocyte-stimulating hormone (MSH), estrogen and progesterone also lead to augmented transcription of tyrosinase and dopachrometautomerase, and lead to augmentation of pigmentation[23,35].

A study in India compared FSH, LH, prolactin, estrogen and progesterone amongst 36 females with melasma and controls of the similar age. There were dissimilarity in the levels of 17 -β- estradiol at the commencement of the menstrual cycle among the groups, proving circulating estrogens may have a role in disease [36].In another study accomplished in Pakistan on 138 females the authors executed serum measurements of estradiol, progesterone and prolactin. The study demonstrated a significant augment in estradiol levels both in the follicular and luteal phases in melasma subjects, in comparison to the controls [37]. Estrogens by acting on nuclear receptors and, in a nongenomic fashion on melanocytes, increases pigmentation [38]. In men, melasma is reported with intake of oral medications that have property to stimulate testosterone production[39].

Expression of hormonal receptors -increase in estrogen receptors(ER) and Progesterone receptors (PR) in diseased skin has been reported. Elevated levels of ER-alpha, ER-beta mRNA was noted in Hyperpigmented lesions in comparison to regular skin as shown by RT-PCR[43-45].

Recommended mechanisms by which estrogen induced melanogenes is occurs are Increase in mRNA appearance of tyrosinase, Trp -1 and Trp- 2 and the activity of tyrosinase melanocytes

1. Activation of cAMP- protein kinase A (PKA) pathway and upregulation of tyrosinase and MITF appearance and activity is also a means by which estrogen improve melanin production[46].
2. Estrogens amplified expression of PDZK1, a member of NHERF family proteins, in both melanocytes and keratinocytes, motivate melanogenesis

and melanosome transport via ERs. Expression of PDZK1 is up regulated in hyper pigmented skin of melasma patients[31]

UV RADIATION-Sun exposure is usually supposed to be the Significant reason and infuriating issue of melasma . The local occurrence of the lesions and aggravation of symptoms on sun coverage propose a sturdy role of UVR in melisma. Frequent occurrence of solar elastosis in diseased skin additionally supports this.

The effects of UV radiation in melasma involve multifaceted cellular interactions and inter play of cytokines and hormones. Apart from melanocytes, other skin mechanism, particularly, keratinocytes, dermal fibroblasts and cutaneous vasculature appear to be concerned in UV radiation provoked melanogenesis.

Effects of UV exposure on melanocytes and keratinocyte derived factors -UV radiation discharges diacylglycerol and arachidonic acid from melanocyte membrane that guide to activation of protein kinase C and enhances melanogenesis. An upregulation in cell surface expression of receptor for keratinocyte - derived melanogenic factors like basic fibroblast growth factor (bFGF), nerve growth factor(NGF),endothelin-1(ET-1),and propio-melanocortin(POMC)- derived peptides, such as melanocyte stimulating hormone(MSH),adrenocorticotrophic hormone(ACTH) and beta - endorphin have been established. Keratinocytes liberate nitric oxide in reaction to UV radiation, and plays a

significant role in melanogenesis intervened by cyclic GMP pathway[51].

Effect of UV radiation on dermal fibroblasts - chronic sun exposure guides to dermal inflammation, elastotic degeneration and dilatation of dermal blood vessels which is seen in the melasma lesions. Fibroblast activation due to dermal inflammation and discharge of a variety of cytokines like the stem cell factor (SCF)and prostaglandins direct to proliferation of melanocytes and melanogenesis. Studies have also shown over expression of cyclo - oxygenase 2 and C-kit in the lesional skin [41,42].

Visible light and melasma- visible light can make alike alterations of Those caused by UV radiation on dark- skinned patients. UV- VL sunscreen (containing iron oxide to protect against VL) demonstrated better development in melasma subjects in comparison to UV- only sun screens suggestive of the function of visible light in melasma[41].

Miscellaneous factors

Vascular Factors in Melasma

Kim et al. confirmed augment in the quantity and dimension of blood vessels in dermis, and upregulation of VEGF, in the diseased skin in comparison with the perilesional normal skin[47]. Increase in vascularisation could be a determinant factor in the appearance of lesions, by stimulation of melanocytes and liberation of vessel growth factors. VEGF appear to augment melanogenesis by enhancing liberation of arachidonic acid metabolites and plasminogen from the dermal

vasculature following interaction with VEGF receptors present over epidermal keratinocytes. The reports of efficacy of two newer treatment modalities that is, tranexamic acid, a plasminogen inhibitor, and pulsed dye laser, which targets mainly vascular components of the skin, add support to the vascular theory of melasma [48].

Melasma affected skin shows augment in vascularity when compared to normal skin. This might be attributable to the raise in the vascular endothelial growth factor (VEGF). UV rays causes up - regulation of the VEGF, beta FGF and interleukin 8. In a study from Korea, it was established that there was noteworthy increase in VEGF and factor VIII a-related antigen in lesional skin compared to adjacent skin and also the pigmentation severity was directly proportional to the vasculature[47].

Neural role in Melasma

Melasma is usually seen over malar and mandibular area along the distribution of the trigeminal nerve. Researches in South Korea in 2009 carried out a relative study amid the involved and adjacent skin biopsies from six Asian Patients. An amplify in the number of Keratinocytes expressing NGFR (nerve growth factor receptor), neural endopeptidase and important nerve fibres in the superficial dermis of the diseased skin was evidenced[73].

Paracrine Influences:

Paracrine cell to cell relation amid keratinocytes, melanocytes and fibroblast also play a significant role in melanogenesis in melasma. UV radiation can cause fibroblast activation and increased release of stem cell factor (SCF), hepatocyte growth factor (HGF), and bFGF leading to increased melanogenesis [50]. There is down regulation of Wnt inhibitory factor-1 (WIF- 1) in fibroblasts or in keratinocytes I that leads to development of melasma by stimulation of melanosome transfer [51].

Melanosomal PH regulates melanin production in process of melanogenesis. The adenosine tri phosphate (ATP) - driven Na+ / Ca2+ upholds an assured pH in melanosomes. The Na+/ Ca2+ - K+ exchanger (NCKX;SLC24), NCKX5 (SLC24A5), and SLC5A2 is expressed in the skin and is established to have key role in human pigmentation. Alpha- MSH or for skolin stimulate the cAMP pathway and leads to alkalization of melanosomes by regulating ion transportation. Recent study identified ion exchangers Na+ / H+ exchanger, cystic fibrosis trans membrane conductance regulator (CFTR), and SLC26A3in estrogen- related hyperpigmentation signalled by PDZK1 molecule[52,53].

Others- Stress has a pronounced effect on melasma. This can be due to the release of factors from adrenal or pituitary gland which in turn augments melanin production[54].

Pigmented cosmetic dermatitis and cosmetics contact sensitivity should be looked for in etiologic factors when melasma is not linked with pregnancy, lactation, or hormone therapy. But, some of these cases

having diffuse to reticulated outline of hyper pigmentation (brown, slate-grey, grey-brown, red- brown, or blue brown depending upon the causal agent) and diagnosed clinically as melasma are perhaps due to pigmented cosmetic dermatitis[55].

The application of cosmetics and ingestion of drugs like anti convulsants and photo sensitizing substance also triggers melasma. Similarly, chemicals such as arsenic, iron, copper, bismuth, silver, gold; and drugs like anti-malarials, tetracyclines, anticonvulsants, amiodarone, sulfonylureas, among others, can cause hyper pigmentation of the skin, by accumulation in the layers of skin or by enhancing melanogenesis[2,56,57].

Diagnosis ofmelasma

The diagnosis can be done by clinical, dermoscopy, RCM, wood'slamp and histopathology examination.

The differentials of melasma are freckles, solar lentigo, toxic melanodermia, Riehl's melanosis, post inflammatory hyperpigmentation, friction melanosis, ochronosis (endogenous and exogenous), and cutaneous erythematosus lupus. Other differential that can be considered are nevus of Ota, café au lait macules, seborrheic keratosis, Civatte's poikiloderma, acquired bilateral nevus of Ota-like macules (Hori's nevus), periorbital hyper pigmentation, erythrose pigmentaire peri buccale of Brocq, erythro melanosis follicularis faciei, facial acanthosis nigricans, drug- induced pigmentation (e.g.: amiodarone) and actinic

lichen Planus[58,59].

Clinical examination

Melasma presents with brownish macules with varying contours and clear margins. It occurs on sun -exposed areas, particularly the face and in less frequently in extrafacial sites like the arms and sternal region. Clinically, epidermal melasma is usually light brown whereas dermal melasma is usually bluish grey and mixed is dark brown in natural light[2].

Wood's lamp

Wood's lamp examination (340 to 400nm) highlights the dissimilarity in pigmentation of the involved skin. Melasmas which show enhancement like epidermal melasma show good response to topical treatments. Other than diagnosing melasma wood' s lamp can predict the therapeutic outcome of melasma [60].

Based on wood' s lamp melasma is classified into four types:

- Epidermal melasma – pigment is accentuated under wood's lamp
- Dermal melasma – no accentuation of the pigmentation under woods lamp
- Mixed – both patterns of epidermal and dermal melasma are noted.
- Indeterminate – seen in skin types V and VI .No clear evidence under wood'slamp.

Dermoscopy

Dermoscopy of melasma (6to 400x) shows key features in skin at a very high magnification. Vascular part, can be visualized which is there

in a most of the patients. The colour strength of melanin and pigment network discloses thickness as well as site of melanin. It appears dark brown color with prominent pigment network when positioned at stratum corneum; light browned shades and network indiscretion of when positioned in basal layer; and bluish- gray colour in dermal layers of skin. It helps in the diagnosis of melasma from other circumstances alike to melasma particularly exogenous ochronosis but also helps in differentiating epidermal from the dermal melasma[61].

RCM

Reflectance confocal microscopy permits the in vivo assessment in melasma when there is significant involvement. It is a non-invasive method. Hypertrophied melanocytes are showed at high resolution. Melanin is noticed in dermis and epidermis, in all cases. RCM is generally used for the diagnosis of pigmented tumors and several inflammatory skin diseases contribution an outstanding association with histologic result. Since melanin is the strongest endogenous contrast of the skin, cutaneous disorders with atypical amounts of melanin appear to be the most appropriate candidates for RCM examination. Particularly, RCM can exactly notice melanocytes, pigmented keratinocytes and melanophages inside epidermis and superficial dermis, thus rising as a suitable instrument for the assessment of melasma [62 - 64].

Histopathologic examination

The melanocytes become visible with large and more outstanding dendrites, cytoplasmic organelles representing that they have elevated activity. The number of melanosomes is also augmented. In the dermis, augmented melanin is present in melanophages, in the upper and middle dermis, where they combined around the dilated blood vessels. The melanophages and the melanin deposition are amplified. There is thin mononuclear infiltrate, mast cells and elastosis. Dermal blood vessels are dilated signifying increased vascularity[64].

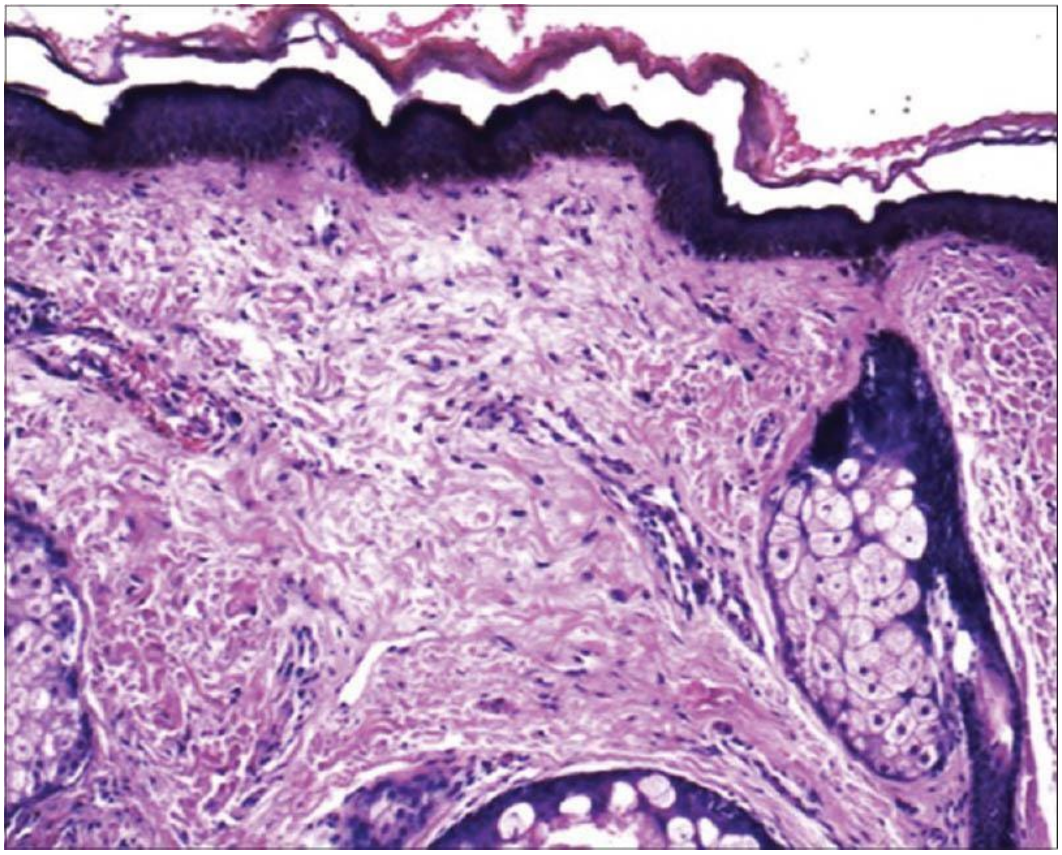


FIGURE 1;H and E, ×200 epidermis shows increased melanin concentration in basal keratinocytes and underlying solar elastosis along with dermal melanophages [65]

Measures to assess the severity of melasma

Colorimetry:

It is an objective evaluation of the severity of melasma. Quantitative and qualitative evaluation of the reaction of a standard source of monochromatic light applied on the skin. Most commonly used method is L*a*b* method – melanin pigmentation is directly relative to lessening in channel L* (luminance); erythema is indicated by channel a* (red-green); variation between yellow and blue is indicated by channel b*. Arctangent (L* - 50/ b*)×(180/ π) is used to compute dimension of individual typological angle (ITA ^{0}), which is done by colorimetry, and is inversely proportional to hyper pigmentation[66].

Mexametry

Mexametry uses a single mono chromatic basis to look for surface reflectance intensities. Erythema as well as melanin indices of the surface will be assesed. Grades are repeatable and sensitive [67].

MASI score [68]

The MASI SCORE was put forward by Kimbrough - Green et al, for the assessment of melasma involving the face. Factors assessed are: 1. Affected area (A)

2. hyperpigmentation(D)

3. Homogeneity of pigmentation (H).

4. Regions of face are assessed ;1.Forehead

2. right malar region

3. Left malar region

4.chin.

Total MASI score: Forehead 0.3 (D+H) A + right malar 0.3 (D+H) A+ left malar 0.3 (D+H) A + chin 0.1 (D+H) A. The final score can be ranged from 0 to48.

Figure 2 : Scheme for calculating MASI score

	0	1	2	3	4	5	6
Darkness of pigment (D): Severity scale (scale 0–4)	None	Slight	Moderate	Marked	Very marked		
Homogeneity of pigment (H): (scale 0–4)	No pigment	Specks	<2 cm patches	>2 cm patches	Homogenous		
Surface area involved (A)		<10%	10%–29%	30%–49%	50–69%	70-89%	90-100%
Site involved	Forehead	Rt. malar	Lt. malar	Chin			
MELASMA AREA (scale 1–6) MA							
Multiplication factors (MF)	0.3	0.3	0.3	0.1			
MA × MF						Total area (A)	

MASI: Melasma area and severity index

Modified MASI total score: [68]

Only Area of involvement (A) and darkness (D) are taken into consideration. Homogeneity is excluded. Score ranges from 0 to 24. mMASI = 0.3A(f) D(f) + 0.3A(lm)D(lm) + 0.3A(rm)D(rm) +A(c) D(c). Here f - forehead, lm - left malar, rm - right malar, c - chin.

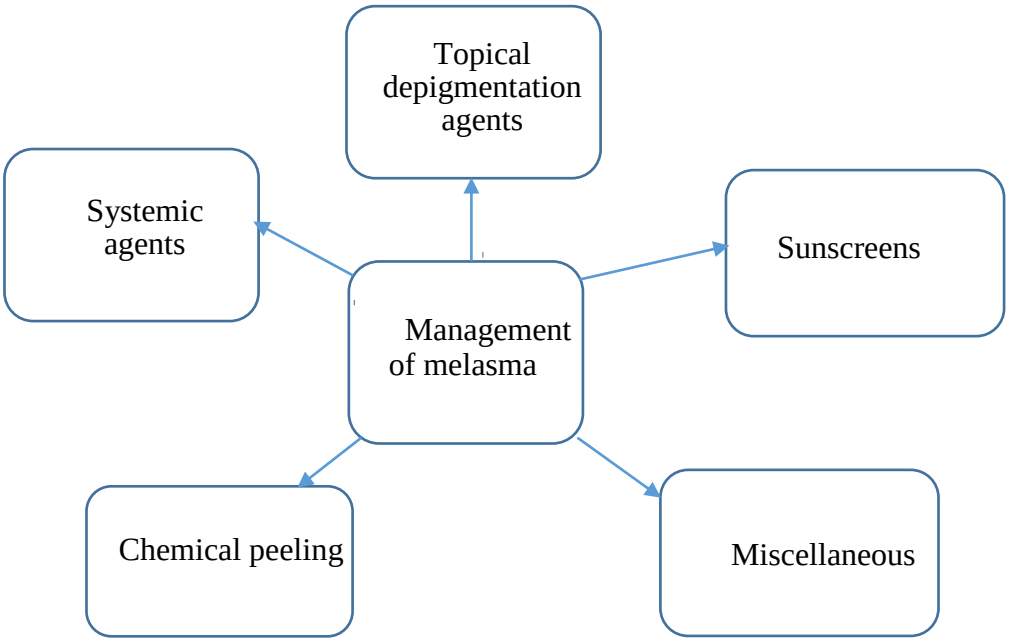
Melasma severity Index: [69, 70]

MSI = 0.4 (a × p 2) l + 0.4 (a × p 2) r + 0.2 (a × p 2) n.

In the formula, "a" stands for " area of involvement," "p" for " severity of pigmentation," "l" for left face, "r"for right face, and " n" for

nose. The area of involvement and severity of pigmentation is scored from 0 to4

TREATMENT OF MELASMA



Melasma a disease which frequently affects the face is always a concern for the affected ones. So the most important part of the treatment is to make the patient understand the avoidance of aggravating factors, the extensive period of treatment and adherence to treatment.

Sun screens

Sunscreens are first line modality of treatments in melasma. The most important trigger for melasma is sun exposure which can be tackled by use of sunscreens

APPLICATION OF SUNSCREENS-[71]

Sunscreens have to be applied to sun exposed parts of the body liberally at a concentration of 2 mg/ cm^2. Repeated applications have to be done at a gap of 2 hours.

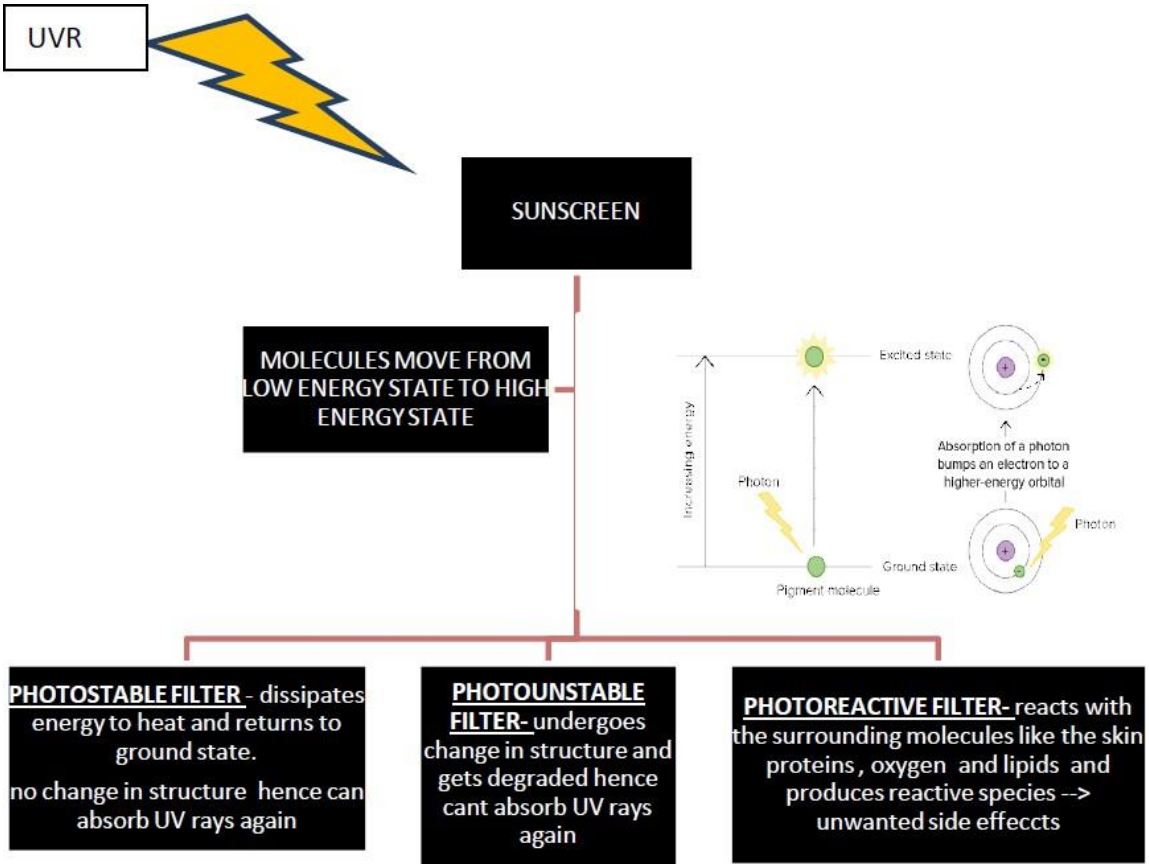


Figure 3 : Mechanism of action of sunscreens[71]

The sunscreens are classified based on UV filters; Inorganic (physical) and organic (chemical) sunscreens[71].

- **Inorganic(physical)sunscreens:**

They function by absorbing, scattering and reflecting the UV rays. They are opaque in nature which produces the whitening effect of the sunscreen.

Zinc oxide and titanium oxide are commonly used inorganic sunscreens.

- **Organic(chemical) sunscreens**:

They absorb UVR of particular wavelength and moves on from a lower energy level to higher energy level. It usually dissipates energy in the form of insensible heat.

Organic sunscreens are further divided into UVB and UVA filters:

1.UVB filter

- PABA derivatives - PadimateO
- Cinnamates - Octinoxate, Cinoxate
- Salicylates - Octisalate, Homosalate, Trolamine salicylate
- Octocrylene
- Ensulizole

2. UVAfilters

- Benzophenones (UVB and UVA2 absorbers) - Oxybenzone, Sulisobenzone, Dioxybenzone
- Avobenzone or Parsol 1789 (UVA1absorber)
- Meradimate (UVA2absorber)

Topical de pigmentation agents

- **Hydroquinone**

Hydroquinone is a di hydroxyl benzene, which has a structure alike to melanin precusors. By blocking tyrosinase enzyme it reverts conversion of DOPA to melanin. HQ influences not only the configuration, melanization, and dilapidation of melanosomes,it also has an effect on the membranous structures of melanocytes and Finally leads to melanocyte necrosis. HQ is approved as gold standard depigmenting medication in the management of epidermal melasma, HQ containing creams (2 to 5%) are used as once daily applications in treating melasma .The de pigmenting effects become obvious in about 5 - 7weeks.

Long term usage of HQ can cause side effects linked to its amount. Irritation is the most frequent side effect. Other side effects include redness, burning sensation, and contact dermatitis, discoloration of nails, depigmentation, and paradoxical PIH. The alleged 'confetti-like' de pigmentation or guttate hypomelanosis is featured by mottled de pigmented spots that expand over melasma lesions. This is seen when HQ creams are used at concentrationof more than 2%. Exogenous ochronosis is seen in darker skin types due to extended use of high concentration creams ,[72-75].

- **Retinoids**

Tretinoin encourages the fast loss of pigment by epidermopoiesis and amplified turnover of epidermis, reduce the contact time amid

keratinocytes and melanocytes. Retinoic acid(RA) decreases UVB-induced pigmentation by decreasing the activity of tyrosinase. RA acts at post transcriptional level on tyrosinase and tyrosinase related protein. In comparison with HQ, RA takes long duration to show effects. It probably shows visible skin lightening effects in 6months Tretinoin monotherapy showed fairly good results in clinical trials but improved results are shown when used in combination with Hydroquinone and corticosteroids. The most frequent side results include redness, burning, stinging, xerosis and flaking. The inflammation can lead to hyper pigmentation, in dark skinned individuals [73,76,77].

- **Topical steroids**

Reversible hypopigmentation of usual skin is disagreeable effect of extended strong steroid application. Melanocytes react to an extensive diversity of chemical mediators. The inhibitory effects of corticosteroids on the synthesis of mediators like prostaglandin and leukotriene may partially clarify their effects on melanogenesis. Unfavorable effects of topical steroids include irritation, rosacea like dermatosis, atrophy, telangiectasia, and hypertrichosis [79].

- **Triple combination:[65]**

It is mixture of topical hydroquinone, tretinoin and steroid. Each element is synergistic with the other; equally side effects are also more when compared to mono therapy. Triple combination is one of the widely used first line therapy for the management of melasma. The first triple

combination formulated by Kligman Willis also known as Kligman' s regimen was introduced in the year 1975.It contains 5% hydroquinone, 0.1% tretinoin and 0.1% dexamethasone.

- Hydroquinone: Demelanising agent that slow down the enzyme tyrosinase thus producing reduction in pigmentation.
- Tretinoin: Prevents oxidation of HQ and increase epidermal diffusion by keratolytic effect melanocyte dispersal and also reduce the atrophy caused by steroid
- Corticosteroid: Reduces irritation caused by the other 2 and also inhibits the melanogenesis by dropping down cellular metabolism [5].

MODIFIED REGIMENS:

1. Modified Kligman's formula **:**It consists of 4% hydroquinone, 0.05% tretinoin and 1% hydrocortisone acetate. Mometasone based triple combination cream was another modification which comprises of 2% hydroquinone, 0.025% tretinoin and 0.1% mometasone. A successful modification with minimal side effect consists of 4% hydroquinone, 0.05% tretinoin and 0.01%fluocinoloneacetonide[80].
2. Pathak's formula **:** which has 2% hydroquinone and 0.05 -0.1% tretinoin
3. Westerhof's formula: which consists of 4.7% N - acetylcysteine, 2% hydroquinone and 0.1% triamcinolone acetonide[79].

- **Azelaic acid**

It inhibits tyrosinase enzyme competitively. Azelaic acid was proposed for use in acne but since it acts on tyrosinase, it is also used in treatment of hyper pigmentary disorders like melasma. Topical azelaic doesn' tcause depigmentation of normal skin and acts only on pigmented skin; because it acts only on abnormal melanocytes. It can be employedfor post inflammatory hyper pigmentation due to acne. Free radicals have a role in inducing hyperpigmentation and azelaic acid acts by decreasing the reduction of free radicals.

A mixture of azelaicacid with tretinoin 0.05% or with glycolic acid 15 to 20% can shower rapid skin lightening. Unfavorable effects of azelaic acid are itching, mild redness, and burning sensation [80-82].

- **Kojicacid**

Kojic acid is obtained from hydrophilic fungal species of Acetobacter, Aspergillus, and Penicillium. It works by restricting the manufacture of free tyrosinase by binding to the copper moiety of tyrosinase and thus inhibits melanogenesis; it is also a potent antioxidant. Kojic (KA) acid is use that concentrations ranging from 1 to 4%.It may cause contact dermatitis and erythema [82 - 84].

- **Arbutin:**

It is a D-glucopyranoside of HQ resultant which is naturally extracted from

bear berry leaves. It inhibits tyrosinase Its synthetic form, deoxyarbutin is more efficacious than arbutin [85].

- **Soy:**

Soy contains active ingredients like protease inhibitors, isoflavones and vitamin E. It inhibits melanosome transfer [86].

- **Vitamin E andC:**

It is a powerful antioxidant that interferes with the lipid peroxidation of melanocyte membranes, inhibits tyrosinase and increases glutathione. When combined with other anti -oxidants, it gives a synergistic effect [85].

Chemical peels

Chemical peels have the ability of causing controlled epidermal lysis and subsequent renewal. The peeling agent causes external effects, i.e., enable elimination of epidermal melanin as well as melanin from the keratinocytes, stops melanosome transport to keratinocytes, hence being an indispensible mode in the treatment of melasma. The type of substance, its amount, number of coats applied and period of application are the chief factors which influence the effectiveness and unfavorable effects as well [87].

Commonly used peels for melasma include glycolic acid, mandelic acid, salicylic acid, tretinoin peel and Jessner' s peel. Chemical peels can be used alone or in combination with other modalities of treatment like topicals, microneedling, lasers

and microdermabrasion Better response is seen when peels are used in mixture with topical therapies. Peels and lasers in darker skin types always pose a danger of Post Inflammatory Hyper pigmentation [87].

CLASSIFICATION OF PEELS: [88,89]

1. Very Superficial light peels: causes necrosis upto stratum corneum level. Agents used: 10% TCA, 30 -50% GA, 20-30%Salicylic acid, 1- 3 coats of Jessner' s solution, 1 - 5%Tretinoin.
2. Superficial light peels: causes necrosis upto level of basal layer. Agents used: 10-30% TCA 1, 50- 70%GA, 4 -7coats of Jessner's solution.
3. Medium depth peels: causes Necrosis upto level of upper reticular dermis. Agents used: 35 - 50% TCA, 70%GA + 35% TCA, phenol unoccluded88%, Jessner's solution +35%TCA, solid CO 2 +35% TCA D.
4. Deep peels: causes Necrosis to a level of mid-reticular dermis. Peels used: Baker- Gordon phenol peel

- Glycolic acid

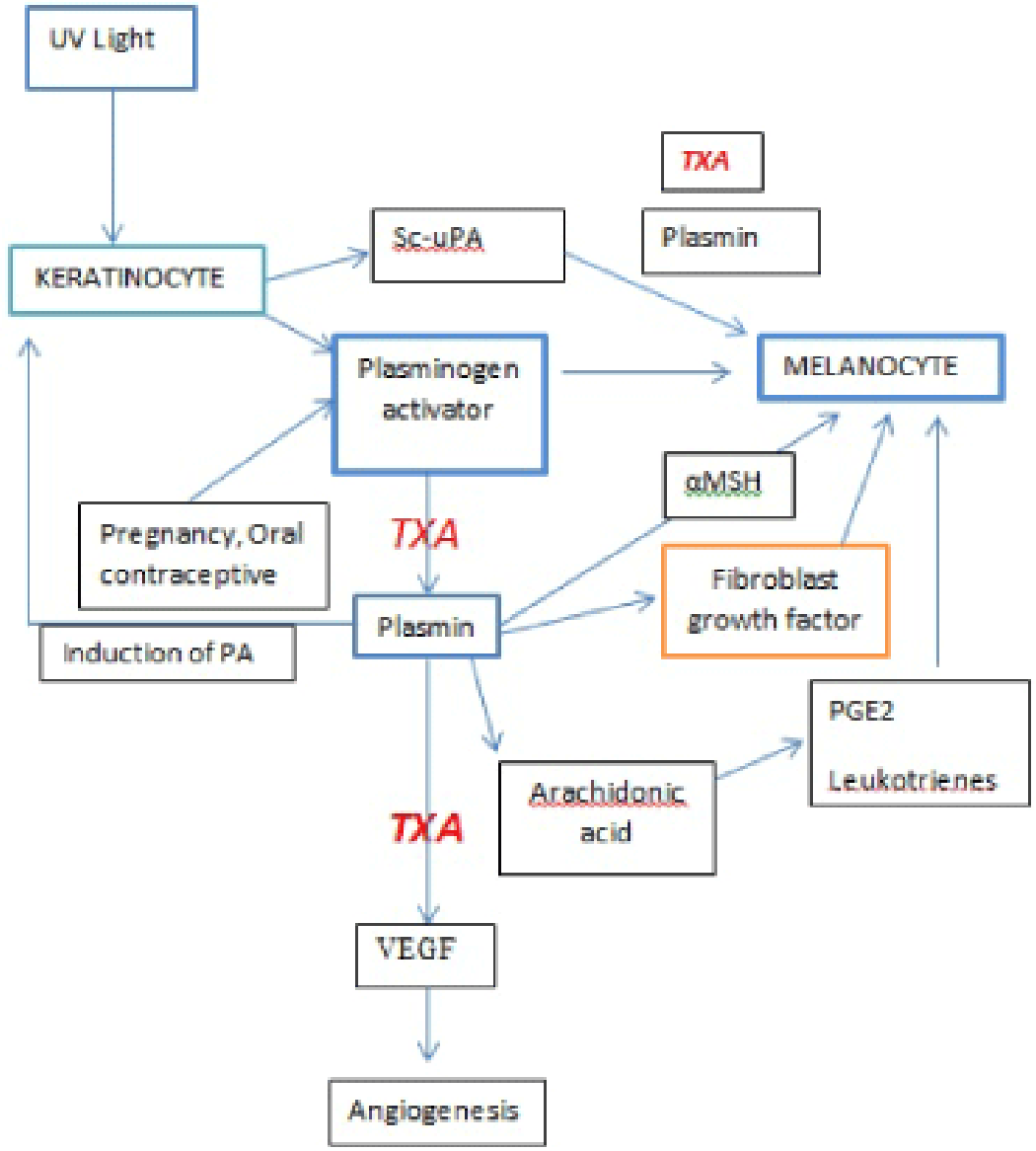
It is most commonly used peeling agent for the treatment of melasma. Glycolic acid is α hydroxy acid that is typically used in combination with other agents at an application of 5 - 10%cream for its skin lightening property .In chemical peeling it is used at various concentrations (35%, 50%, 70%).It causes epidermal remodeling and augmented desquamation, leading to faster pigment dispersal on pigmented lesions. It reduces melanin synthesis in melanocytes by

inhibiting tyrosinase. Irritation is frequently noted which can be decreased by applying topical moisturizer [90].

Systemic agents

Tranexamic acid –is used in oral, topical and intra dermal routes for the treating melasma. TXA is lysine amino acid derivative that lessen the dissolution of fibrin. TXA shows its anti fibrinolytic effects by reversible blockage of **lysine** binding sites on plasminogen. This averts plasmin from relating with lysine residues on the fibrin that leads to succeeding fibrin degradation. The human plasminogen has4– 5 lysine attaching sites. Though, their attraction for TXA is less. The high affinity site for lysine binding of plasminogen is concerned in its attatchment to fibrin. Plasminogen gets relocated from its fibrin attachment after the high affinity binding site is saturated with tranexamic acid. Although plasmin may be formed due to conformational changes in plasminogen, binding to and dissolution of the fibrin matrix is inhibited. TXA is excreted unchanged in the urine[91,92].

Figure 4 - Mechanism of action of tranexamic acid [93].



TXA- tranexamic acid; PA- Plasminogen Activator; uPA- urokinase PA

Inhibition of ultraviolet‐induced plasmin activity

UV exposure accentuates plasminogen activator production by

epidermal keratinocytes in situ. TXA is a plasmin inhibitor that blocks the conversion of plasminogen to plasmin. The drug accomplishes this through the inhibition of plasminogen activator by creating a reversible complex with plasminogen. TXA also prevents the attachment of plasminogen to the keratinocytes and thus slow down UV induced plasmin activity in keratinocytes. Plasmin augments the liberation of arachidonic acid (AA) and alpha -melanocyte-stimulating hormone (α-MSH) intracellularly. AA and α -MSH have melanogenesis stimulating properties. Thus Tranexamic acid by plasmin inhibition reduce the keratinocyte pool of AA concerned in UV induced melanogenesis[94-98].

Reduction in prostaglandin production

On UV exposure, prostaglandins (PGs) activate various signalling pathways that are involved in growth, differentiation, and apoptosis of melanocytes. TXA inhibits PG production and thus reduces the melanocyte tyrosinase activity. This particular characteristic of TXA is successfully applied in the treatment of melasma, UV induced hyperpigmentation, and other Post inflammatory hyperpigmentation [99].

Reduction of vascularity in melasma

UVR enhances production of angiogenic factors like vascular endothelial growth factor (VEGF), basic fibroblast growth factor, and inter leukin- 8.VEGF interacts with VEGF receptors in keratinocytes of epidermis and discharges

metabolites of AA and plasminogen from the proliferated vessels. This enhances melanogenesis. TXA targets these vascular components of the skin and hence adds support to the vascular theory of melasma.

Plasmin plays an important role in the release of b-FGF, which is a potent melanocyte growth factor and promotes melanocyte proliferation. TXA indirectly reduces b-FGF production. It also has effect on angiogenesis and neo vascularization induced by b-FGF[47,64,100].

Effects on melanogenesis

Tyrosinase-related protein(TRP-1)and TRP-2 are key enzymes in the Raper mason pathway of melanogenesis. TXA reduces tyrosinase levels and also levels of TRP-1 and TRP-2. Activation of the signaling pathway extracellular signal-regulated kinase(ERK) provokes microphthalmia-associated transcription factor (MITF) degradation, ensuing in decreased melanogenesis. MITF is the transcription factor regulating these enzymes concerned in melanogenesis. TXA stimulates the ERK signaling pathway and downregulates MITF protein level. This reduces inflammation - induced melanogenesis by decreasing tyrosinase protein expression. TXA is also capable of suppressing melanogenesis by regulating tyrosinase transcription in addition to an anti-inflammatory action [94,98].

DOSE [101] - It is administered as oral formulation at a dose of 250

mg BD, Topically as 2% emulsion, 3% cream, and 5% solution and intradermal injections are given at a concentration of 4mg/ ml.

Side effects

Topical TXA – minimal side effects are reported. They include erythema, stinging, burning ,xerosis Oral tranexamic acid: in melasma low dose of TXA is used hence side effects are minimal which include nausea, diarrhoea, oligomenorrhoea ,palpitations at high doses –venous Thromboembolism, CVA and pulmonary embolism has been reported Intradermal – pain, edema, burning[91].

Table 4: Studies showing effectiveness of TA

Study	Conclusion
Karn et al[98]	Notable reduction in mean MASI
Wu et al[97]	65% have shown to have major improvements
Na et al[48]	Decreased basal melanin formation and dermal changes were reversed
Amir and Naseem[102]	63% showed better results
Li et al[103]	4^{th}, 12^{th} and16^{th} week improvements were there
Padhi et al[104]	Faster and constant improvement
Tan et al[105]	Low dose oral TA is better
Lee et al[106]	90% reported to have noteworthy changes

Glutathione [107]

Glutathione, a low molecular weight thiol peptide plays a significant role in maintaining the intracellular redox balance, itself being a powerful antioxidant. Recently, it is being promoted as a systemic skin lightening means for the management of several conditions including melasma. Glutathione exerts its hypopigmentary effect by several mechanisms namely direct (by binding with the copper-containing active sites) and indirect(via antioxidant effect leading to exhaustion of free radicals and peroxides) inhibition of tyrosinase enzyme (the key enzyme for melanogenesis).

L- Cysteine peptide

It is another remarkable antioxidant which may be used for the management of melasma due to its skin-lightening property. It is claimed to be 3 –5 times more powerful than glutathione. Elevated concentration of this molecule inhibits the tyrosinase enzyme (rate limiting enzyme for melanogenesis) and promotes pheomelanin synthesis by forming cysteinyl- dopa. L- Cysteine may be obtained from natural sources such as poultry, yoghurt, egg yolks[108].

Laser and Light Therapies [109]

LASER (an acronym; Light Amplification by Stimulated Emission of Radiation) gives an insight to its creation. Laser is emission of a radiation which is stimulated, and light amplifies it further.

Laser and light therapy represent an alternative third-line approach to treat

melasma and may be particularly beneficial for patients with melasma that is refractory to topical therapy or chemical peel regimens, or when a patient wishes for an accelerated pace of improvement. Analogous to chemical peels, these modalities accelerate the removal of pathways for melanin but do not target the melanin production itself.

Intense pulsed light

IPL therapy uses a flash lamp light source that emits non coherent light with wavelengths between 515 nm and 1200 nm. Filter sets allow for the targeting of selective chromophores (melanin vs. hemoglobin) and has been used to treat various pigmentary disorders.

IPL therapy appears to give modest improvement in patients with melasma that is refractory to topical therapy alone but have a modest recurrence rate unless an aggressive topical therapy is maintained at least 6 to 12 months post-treatment. IPL therapy is best suited to treat patients with Fitzpatrick skin types 1 to 3 because use with patients who have a darker skin type carries an elevated risk to target normal endogenous skin pigment.

Patients with epidermal melasma may respond more favorably to IPL therapy compared with those with mixed or dermal melasma.

Combination of Laser Toning and IPL

“Laser toning” with Q-switched Nd:YAG 1064-nm laser combined with IPL for the treatment of melasma has been reported to enhance the efficaciousness of the

two individual procedures. Skin toning with the QS Nd:YAG laser targets deeper pigment, while IPL targets a wide range of superficial cutaneous structures. [110]

Picosecond lasers[111]

Recent innovations in laser design have introduced a new class of lasers that generate picosecond-domain pulses. Shorter laser pulse durations result in pigment fragmentation that is more a result of photoacoustic than photothermal effects.

Therefore, it may be more efficient at pigment removal without inducing thermal damage to surrounding tissue.

This thermal damage seems to be the greatest drawback of conventional Q-switched laser treatment for patients with melasma and likely the cause of the high PIH rates after treatment. Picosecond lasers are currently available with laser outputs of 532 nm, 755nm, and 1064 nm. More recently, fractionated picosecond hand pieces have been developed for the purpose of resurfacing and rejuvenation.

Only a few clinical studies have been completed with these new devices and thus far, no results with regard to melasma have been reported. Due to the potential of picosecond lasers to work via photoacoustic mechanisms, they may present a new treatment modality that is suitable for patients with melasma.

Pulsed Dye and Copper Bromide Lasers

The vascular lasers were used to treat melasma with variable results. There are not enough good scientific reports to confirm the role of vascular laser and copper

bromide lasers for the treatment of melasma .

Nd-YAG Lasers[112]

Q-Switched laser have output in nano sec range with high peak power. “Q” stands for quality factor of a resonant circuit. Switching “Q” means varying the circuit quality to store the energy or let it out.

Mechanism of action of Q-Switch lasers:

Q switching is a method for obtaining energetic pulses from lasers by modulating the intracavity losses. It is a technique for obtaining energetic short (but not ultra short) pulses from a laser by modulating the intracavity losses, the so-called the Q factor of the laser resonator. The technique is mainly applied for the generation of nanosecond pulses of high energy and peak power with solid-state bulk lasers. These giant pulses are responsible for the unique laser-tissue interaction that is seen with QS lasers.

Q-switched lasers work on the principle of selective photothermolysis and also produce an additional photoacoustic effect producing shock waves that cause explosion of target. Very high energy, to the tune of 300 megawatts, is delivered in a very short period of time (5–100 ns) which leads to rapid thermal expansion. This produces shock waves that rupture the targets such as melanosomes and ink particles.

The ruptured fragments are cleared by tissue macrophages either to the lymphatic channels or to the regional lymph nodes. Some fragments may be eliminated trans-epidermally. To be selective, the pulse duration of the laser should match the thermal relaxation time (TRT) of the target. The estimated TRT of epidermis is 1–10 ms and the TRT of tattoo ink particles is 0.1–10 ns, although some

newer estimates are in the range of 10–100 picoseconds. The size of the tattoo ink particles is about 10–100 nm and is generally placed at a depth of 1.1–2.9 mm. Laser tissue interaction produces intracellular steam and vacuole formation, which leads to immediate whitening. An audible popping sound is heard during the procedure due to the photo-acoustic effect.

INDICATIONS:

Epidermal lesions:

- CALM
- Lentigines
- Freckles
- Solar lentigo
- Nevus spilus
- Pigmented seborrheic keratosis
- DPN
- Melasma

Dermal lesions:

- Nevus of Ota
- Melasma
- Blue nevus
- Hori's nevus (acquired bilateral nevus of Ota-like macules)
- Tattoos—amateur, professional, cosmetic, medicinal and traumatic

Epidermal-dermal lesions:

- Post inflammatory hyperpigmentation
- Nevus spilus
- Periorbital pigmentation
- Perioral pigmentation
- Acquired melanocytic nevi(moles)
- Melasma
- Becker'snevus

Contraindications :

Absolute:

- Associated photoaggravated skin diseases and medical illness, for example, SLE.
- Treatment area with active cutaneous infections, for example, herpes labialis, staphylococcal infections.
- Unstable vitiligo and psoriasis for risk of koebnerization of treated area.
- Tattoo granuloma.
- Allergic reactions

Relative:

- Keloid and keloidal tendencies.
- Patient on isotretinoin.
- History of herpes simplex/history of herpes for increased risk of reactivation: This risk should be seriously considered prior to performing the procedure. If the treating physician decides to perform the procedure,

the risk and benefit should be explained to the patient and the procedure should be performed after proper informed consent and only after a course of acyclovir.

- Patient who is not cooperative or has unrealistic expectation

MATERIALS AND METHODS

MATERIALS AND METHODS

METHODOLOGY

This study was carried out in the outpatient clinic of Dermatology, Venereology and Leprosy in R L Jalappa Hospital and Research centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar from November 2018 to July2020 in patients with melasma. A total of 64 patients with melasma (32 in each group) were included in this study.

This was a hospital based interventional study.

Inclusion criteria:

All patients in the age group years 18 -50 from either gender from the outpatient department diagnosed with melasma were included in the study.

Exclusion criteria:

- Lactating and pregnant women were excluded.
- Patients with any systemic co morbidities, bleeding disorders, patients on anticoagulants, any drug allergy to the study drug were excluded.

Data collection tools and techniques-

- All patients who fulfills the selection criteria was allocated and divided into group A and B by block randomization
- Informed consent was obtained from the patient after explaining the details of the study.
- Demographic data like name, age, address and telephone number were

recorded.

- A detailed history including patient details, chief complaints related to skin, onset and duration of disease and associated medical or skin disorders were noted.
- MASI scoring was done and baseline photographs were taken
- Group A patients received intralesional tranexamic acid once per week for4 weeks.
- Tranexamic acid is available as 5 mL ampoule containing 500 mg of the drug. After gentle cleansing, topical EMLA cream will be applied over the area to be treated for about 45 to 60 min an d then treated with multiple microinjections of TA (4mg/ mL) intradermally into the melasma lesions at 1 cm intervals, depending on the extent of involvement. Tranexamic acid dilution of 0.4 ml will be injected intradermally into the lesions of melasma. A Tranexamic acid dilution of 0.0525mg/ml was prepared using insulin syringe with 3 units of tranexamic (TA 100 mg/ml) and 37 units of sterile water and one ml of 0.0525 mg/ml of Tranexamic acid was administered.
- Group B patients were administered 1064-nm QSNYL is 6-8 mm SS, 10 Hz, 0.5-1J/ cm 2, 10 passes at once in two weeks for a total of 4 weeks. Treatment is performed with the hand piece held perpendicular to skin surface with minimum overlap. The entire lesion is covered in a single pass. All person in the laser room must wear appropriate eye protection glasses during the treatment. Increment of 0.1 J/ 3 weeks is done .The treatment was given For three sittings at a gap of two weeks. Passes are stopped in case of immediate lightening or mild erythema of skin. Ice cubes were applied after the procedure. Sun screen were applied and

advised to strict sun protection in day time.

- All patients were advised to apply broad spectrum sunscreens during daytime with an SPF of 30 at 2 hourly intervals.
- Post treatment evaluation was done with detailed history, clinical examination, melasma area severity index(MASI) scoring, and colour photographs. The evaluations were taken at baseline, 2 weeks and 4 weeks after treatment.

STATISTICAL METHODS USED FOR DATA ANALYSIS

Statistical analysis:

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test or Fischer's exact test** (for 2x2 tables only) was used as test of significance for qualitative data.

Continuous data was represented as mean and standard deviation. **Independent t test** was used as test of significance to identify the mean difference between two quantitative variables.

Paired t test is the test of significance for paired data.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs

P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data

Sample size calculation:

Sample size is based on the difference in MASI score in epidermal melasma in a study "A comparative of lowfluence 1064-nm Q- switched Nd YAG laser with topical 20% Azelaic acid cream and their combination in melasma in Indian patients" in year 2012 observed an average variance estimate of 5.41 in MASI score at 12 weeks in comparing Nd:YAG laser with 10% Azelaic acid. In the presence of study instead of Azelaic acid, Tranexemic acid will be used to find an effect size of 10% Tranexemic acid in MASI score at 12 weeks between laser and Tranexemic acid with 95% confidence interval 80% power with alpha error of 5%. The calculated sample size per group will be 26. Expecting a drop out rate of 20% during the follow up the final sample per group is estimated as 26+6 =32.

$$\text{Sample size} = \frac{Z_{1-\alpha/2}{}^2\, p(1-p)}{d^2}$$

Here

$Z_{1-\alpha/2}$ = Is standard normal variate (at 5% type 1 error ($P<0.05$) it is 1.96 and at 1% type 1 error ($P<0.01$) it is 2.58). As in majority of studies P values are considered significant below 0.05 hence 1.96 is used in formula.
p = Expected proportion in population based on previous studies or pilot studies.
d = Absolute error or precision – Has to be decided by researcher.

Sample size: 32 in each group. Total = 64.

Method of collection of data (including sampling procedure)

Block randomisation technique

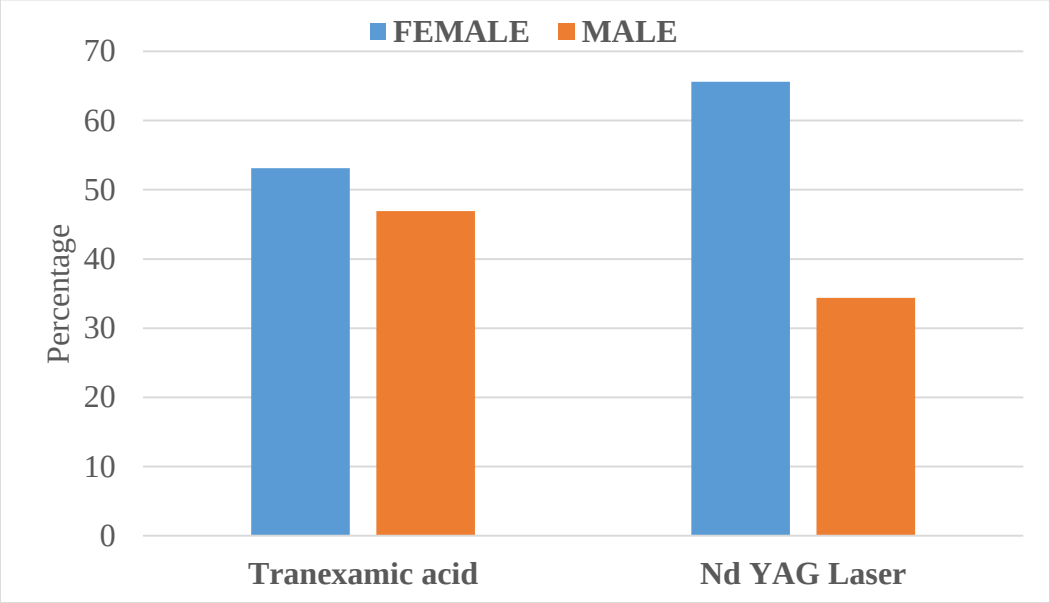
RESULTS

RESULTS

Table 5:- Distribution of subjects according to sex between groups

	Group		Total
	Tranexamic acid	Nd YAGLaser	
Male	15	11	26
	46.9%	34.4%	40.6%
Female	17	21	38
	53.1%	65.6%	59.4%
Total	32	32	64
	100.0%	100.0%	100.0%

P Value 0.309, there was no statistically significant difference found between groups with respect to sex. Among subjects with treatment Tranexamic acid 53.1% of the subjects were female and 46.9% of the subjects were male. Among subjects with treatment Nd YAG laser 65.6% of the subjects were female and 34.4% of the subjects were male.

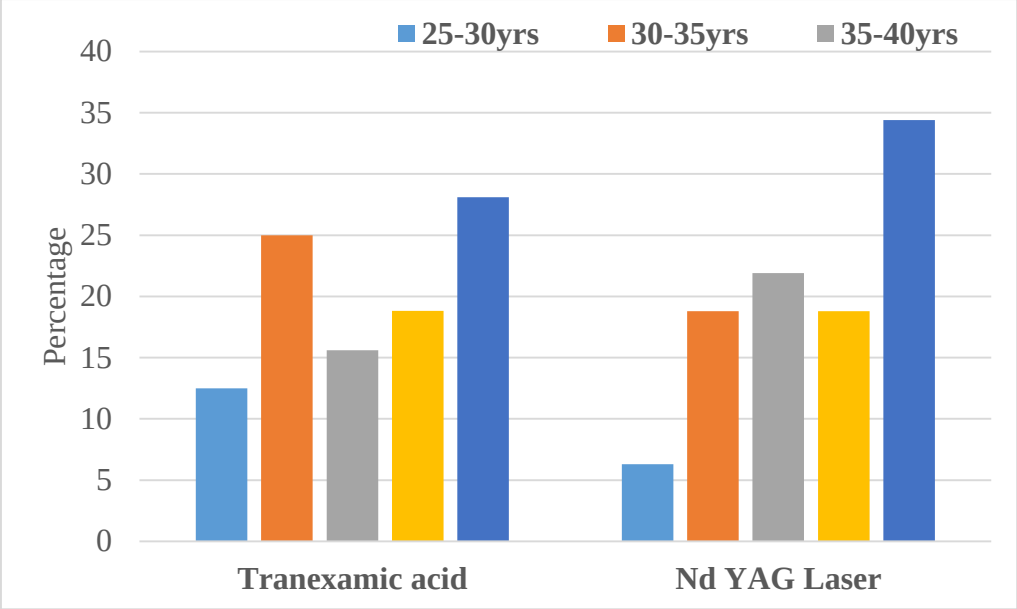


Graph 1:- Graph showing Distribution of subjects according to sex between groups

Table 6:- Distribution of subjects according to age group between groups

	Group		Total
	Tranexamic acid	Nd YAGLaser	
25-30yrs	4	2	6
	12.5%	6.3%	9.4%
30-35yrs	8	6	14
	25.0%	18.8%	21.9%
35-40yrs	5	7	12
	15.6%	21.9%	18.8%
40-45yrs	6	6	12
	18.8%	18.8%	18.8%
45-50ysr	9	11	20
	28.1%	34.4%	31.3%
Total	32	32	64
	100.0%	100.0%	100.0%

P Value 0.829, there was no statistically significant difference found between groups with respect to age. Among subjects with treatment Tranexamic acid 28.1% of the subjects were in 45-50yrs age group followed by 25% of the subjects were in 30-35yrs age group, 18.8% of the subjects were in 40-45yrs age group , 15.6% of the subjects were in 35-40yrs age group and 12.5% of the subjects were in 25-30yrs age group. Among subjects with treatment Nd YAG laser 34.4% of the subjects were in 45-50yrs age group followed by 18.8% of the subjects were in 30-35yrs age group, 18.8% of the subjects were in 40-45yrs age group,21.9% of the subjects were in 35-40yrs age group and 6.3% of the subjects were in 25-30yrs age group



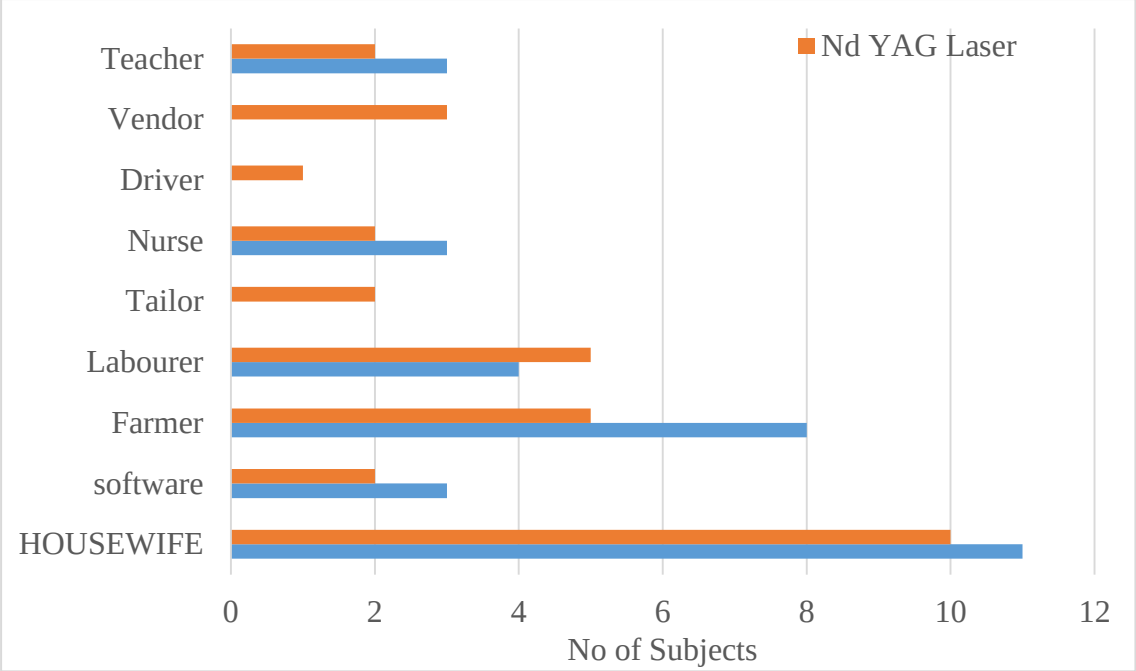
Graph 2:- Graph showing Distribution of subjects according to age group

Table 7:- Distribution of subjects according to occupation between groups

	Group		Total
	Tranexamic acid	Nd YAGLaser	
Housewife	11	10	21
	34.4%	31.3%	32.8%
Software	3	2	5
	9.4%	6.3%	7.8%
Farmer	8	5	13
	25.0%	15.6%	20.3%
labourer	4	5	9
	12.5%	15.6%	14.1%
Tailor	0	2	2
	.0%	6.3%	3.1%
Nurse	3	2	5
	9.4%	6.3%	7.8%
Driver	0	1	1
	.0%	3.1%	1.6%
Vendor	0	3	3
	.0%	9.4%	4.7%
Teacher	3	2	5
	9.4%	6.3%	7.8%
Total	32	32	64
	100.0%	100.0%	100.0%

Majority of the subjects were housewife followed by farmer by occupation in both groups.

P value 0.489, there was no statistically significant difference found between groups with respect to occupation.



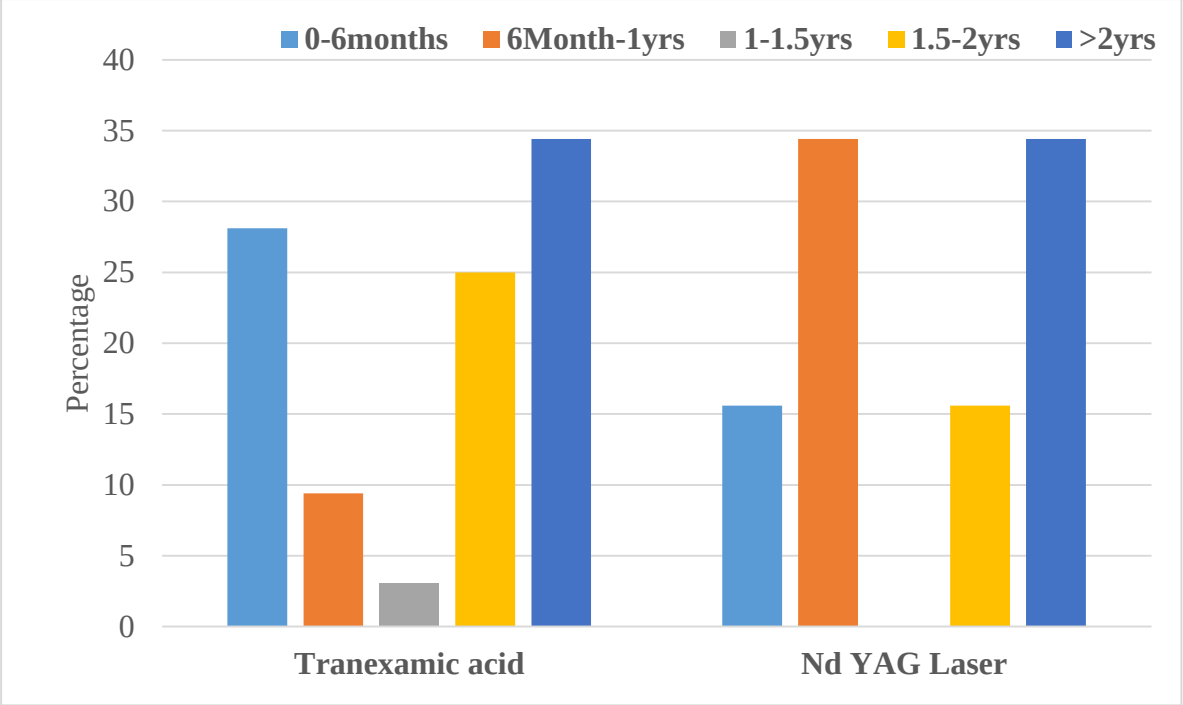
Graph 3:- Graph showing Distribution of subjects according to occupation.

Table 8:- Distribution of subjects according to duration of disease

	Group		Total
	Tranexamic acid	Nd YAGLaser	
0-6months	9	5	14
	28.1%	15.6%	21.9%
6month-1yrs	3	11	14
	9.4%	34.4%	21.9%
1-1.5yrs	1	0	1
	3.1%	.0%	1.6%
1.5-2yrs	8	5	13
	25.0%	15.6%	20.3%
>2yrs	11	11	22
	34.4%	34.4%	34.4%
Total	32	32	64
	100.0%	100.0%	100.0%

Majority of the subjects had duration of disease for more than >2yrs followed 0-6 months in Tranexamic acid group whereas in group Nd YAG laser Majority of the subjects had duration of disease more than >2yrs followed 6months- 1yrs.

P value 0.116, there was no statistically significant difference found between groups with respect to duration of disease.



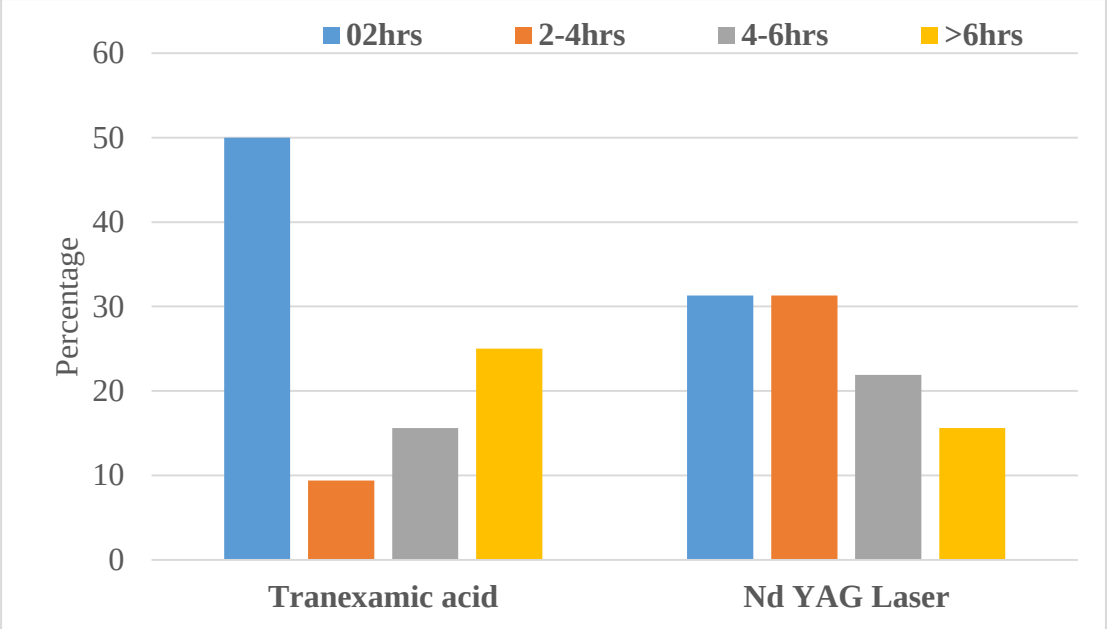
Graph 4:- Graph showing Distribution of subjects according to duration of disease

Table 9:- Distribution of subjects according to duration of exposure to sunlight

	Group		Total
	Tranexamic acid	Nd YAGLaser	
0-2hr	16	10	26
	50.0%	31.3%	40.6%
2-4hr	3	10	13
	9.4%	31.3%	20.3%
4-6hr	5	7	12
	15.6%	21.9%	18.8%
>6hrs	8	5	13
	25.0%	15.6%	20.3%
Total	32	32	64
	100.0%	100.0%	100.0%

Majority of the subjects had duration of exposure to sunlight between 0-2hrs followed >6hrs in Tranexamic acid group whereas in group Nd YAG laser the subjects had duration of exposure to sunlight between 2-4hrs, 0-2hrs equally followed by 4-6hrs.

P value 0.103, there was no statistically significant difference found between groups with respect to duration of sun exposure.

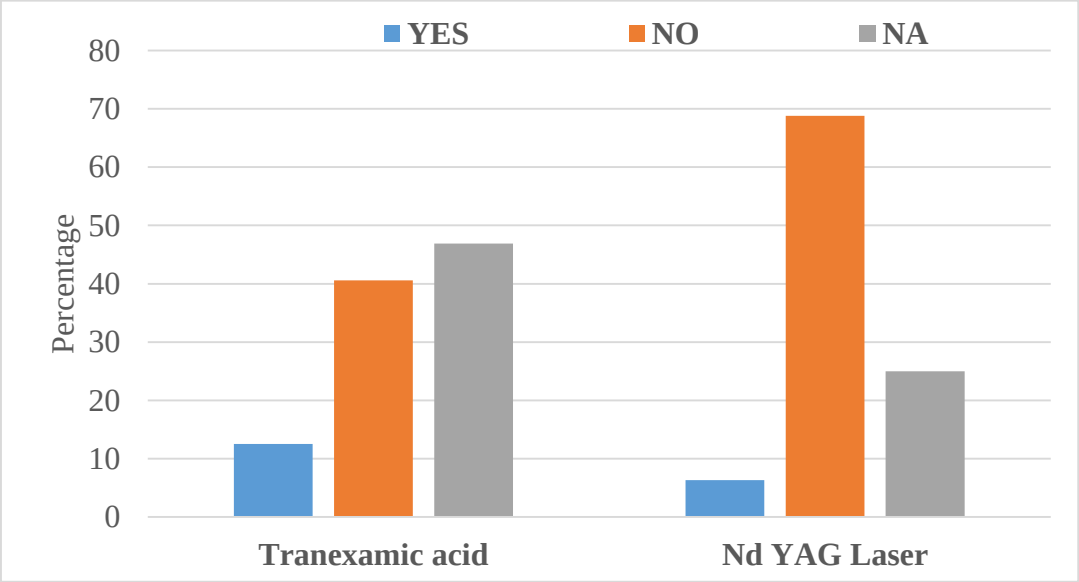


Graph 5:- Graph showing Distribution of subjects according to duration of exposure to sunlight.

Table 10:- Distribution of subjects according to OCP usage

	Group		Total
	Tranexamic acid	Nd YAGLaser	
Yes	4	2	6
	12.5%	6.3%	9.4%
No	13	22	35
	40.6%	68.8%	54.7%
NA	15	8	23
	46.9%	25.0%	35.9%
Total	32	32	64
	100.0%	100.0%	100.0%

P value 0.078, there was no statistically significant difference found between groups with respect to OCP usage.

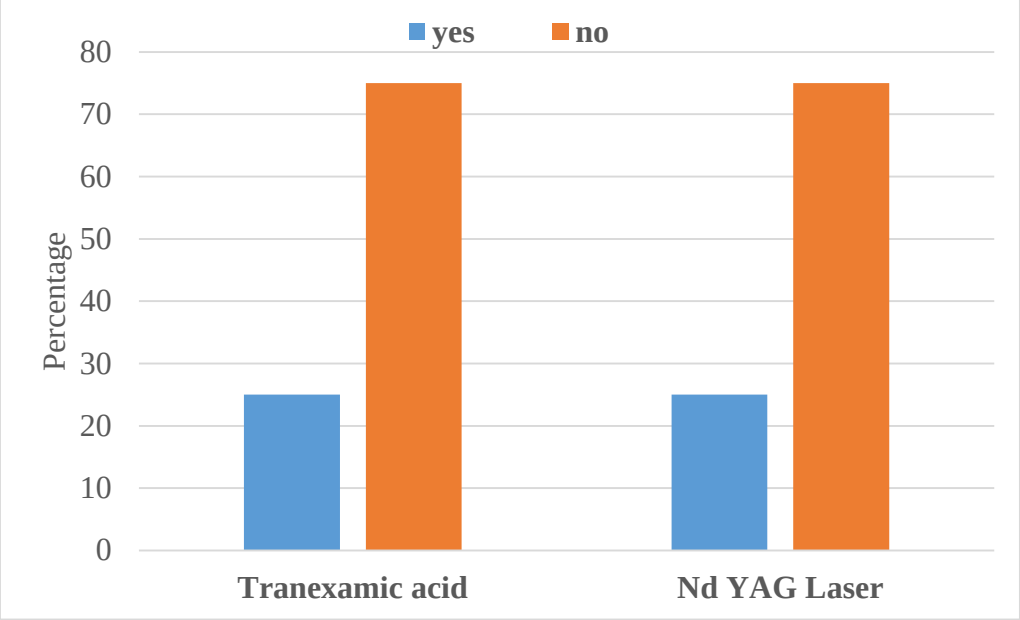


Graph 6:- Graph showing Distribution of subjects according to OCP usage.

Table 11:- Distribution of subjects according to usage of cosmetics

	Group		Total
	Tranexamic acid	Nd YAG Laser	
Yes	8	8	16
	25.0%	25.0%	25%
NO	24	24	48
	75.0%	75.0%	75%
Total	32	32	64
	100.0%	100.0%	100.0%

P Value 1.00, there was no statistically significant difference found between groups with respect to usage of cosmetics. Among subjects with treatment Tranexamic acid25% of the subjects had used cosmetics and 75% of the subjects were didn't used. Among subjects with treatment Nd YAG laser 25% of the subjects had used cosmetics and 75% of the subjects were didn't used

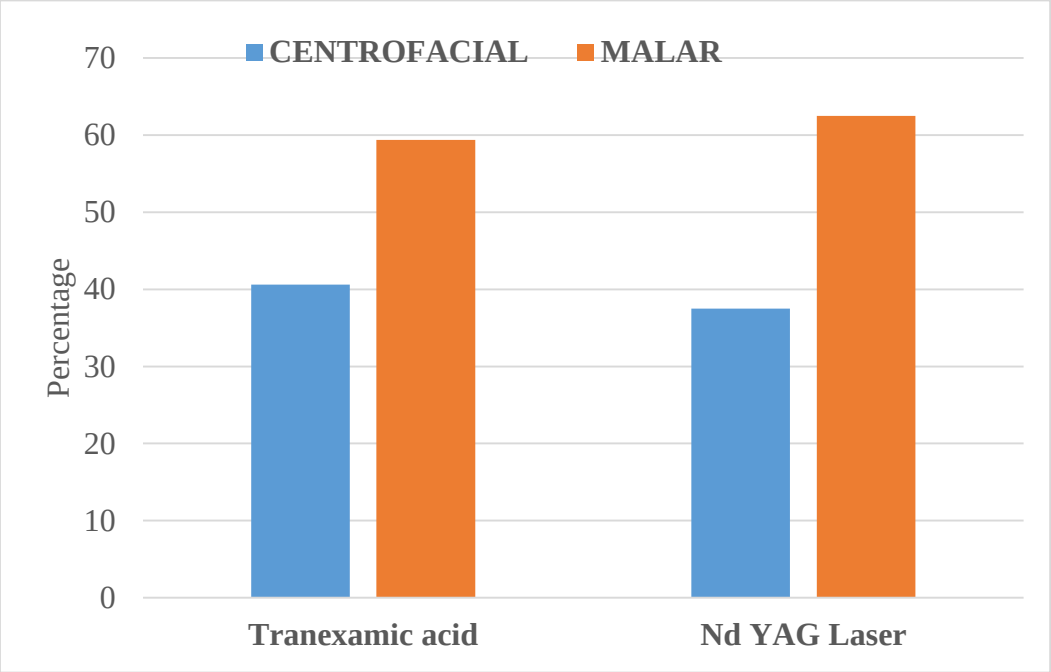


Graph 7:- Graph showing Distribution of subjects according to cosmetic usage

Table 12:- Distribution of subjects according to type of melasma

	Group		Total
	Tranexamic acid	Nd YAG Laser	
Centro facial	13	12	25
	40.6%	37.5%	39.1%
Malar	19	20	39
	59.4%	62.5%	60.9%
Total	32	32	64
	100.0%	100.0%	100.0%

P Value 0.798, there was no statistically significant difference found between groups with respect to type of melasma. Among subjects with treatment Tranexamic acid 59.4% of the subjects had malar and 40.6% of the subjects had centro facial melasma. Among subjects with treatment Nd YAG laser 62.5% of the subjects had malar and 37.5% of the subjects had centro facial melisma

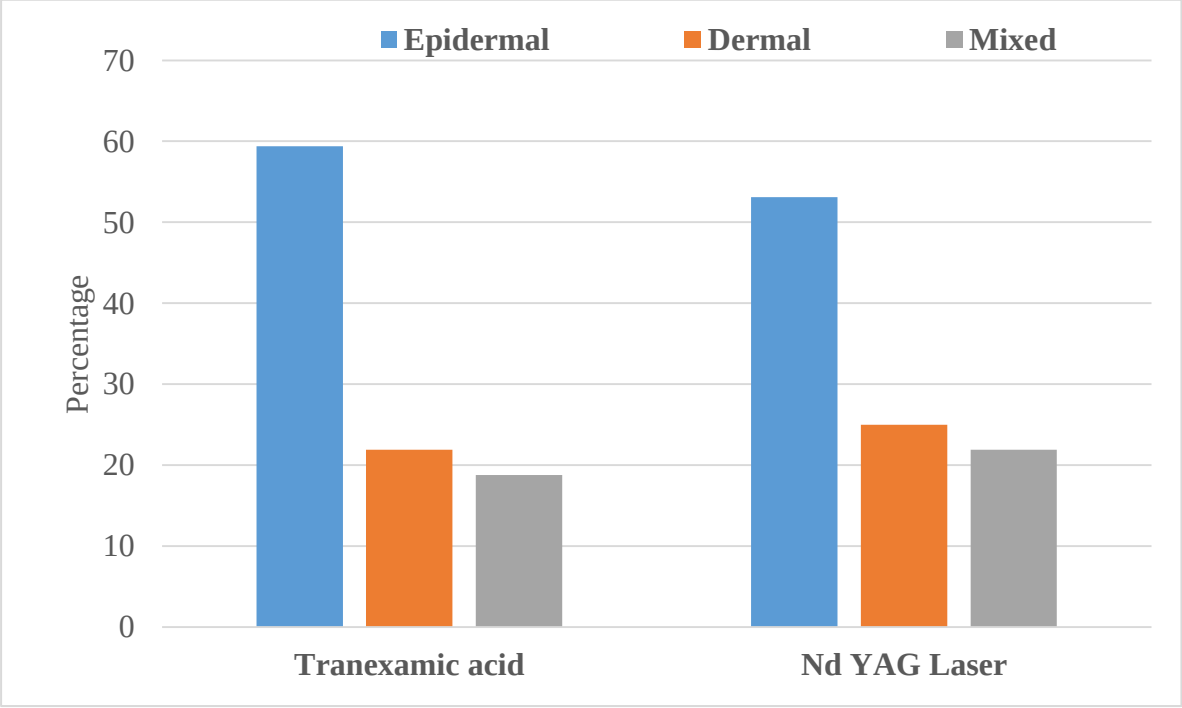


Graph 8:- Graph showing Distribution of subjects according to type of melasma

Table 13:- Distribution of subjects according to woods lamp examination

	Group		Total
	Tranexamic acid	Nd YAG Laser	
Epidermal	19	17	36
	59.4%	53.1%	56.3%
Dermal	7	8	15
	21.9%	25.0%	23.4%
Mixed	6	7	13
	18.8%	21.9%	20.3%
Total	32	32	64
	100.0%	100.0%	100.0%

P value 0.888, there was no statistically significant difference found between groups with respect to woods lamp examination

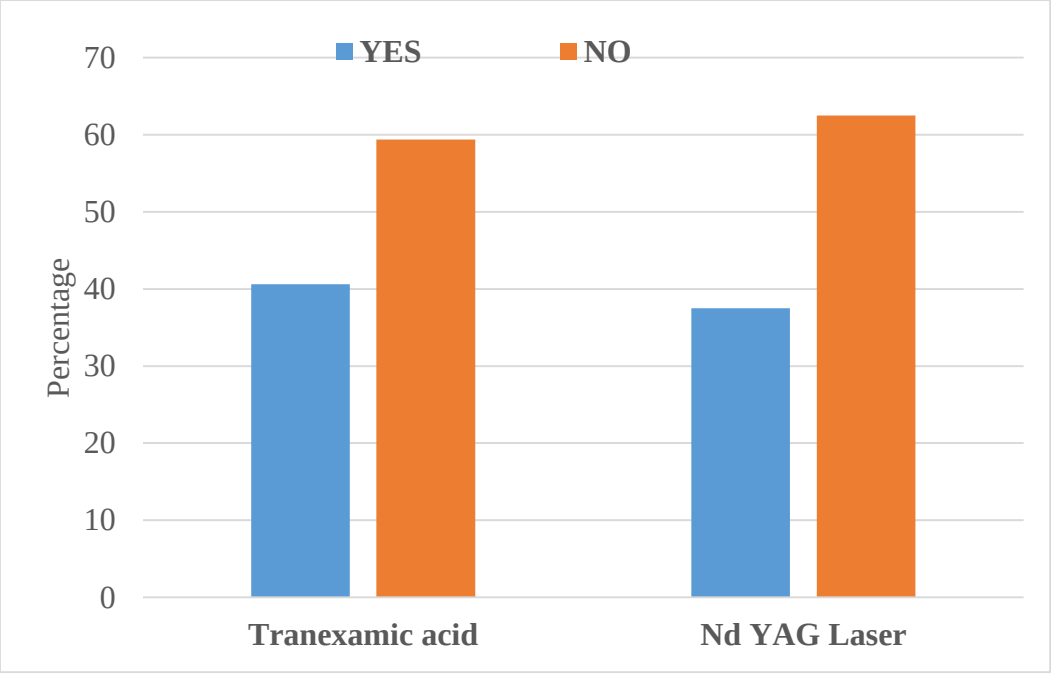


Graph 9:- Graph showing Distribution of subjects according to woods lamp examination.

Table 14:- Distribution of subjects according to recurrence

	Group		Total
	Tranexamic acid	Nd YAGLaser	
Yes	14	10	24
	43.8%	31.3%	37.5%
No	18	22	40
	56.3%	68.8%	62.5%
Total	32	32	64
	100.0%	100.0%	100.0%

P Value 0.302, there was no statistically significant difference found between groups with respect to recurrence. Among subjects with treatment Tranexamic acid 43.8% of the subjects had recurrence and 56.3% of the subjects did not had. Among subjects with treatment Nd YAG laser 31.8% of the subjects had recurrence and 68.8% of the subjects did not had.

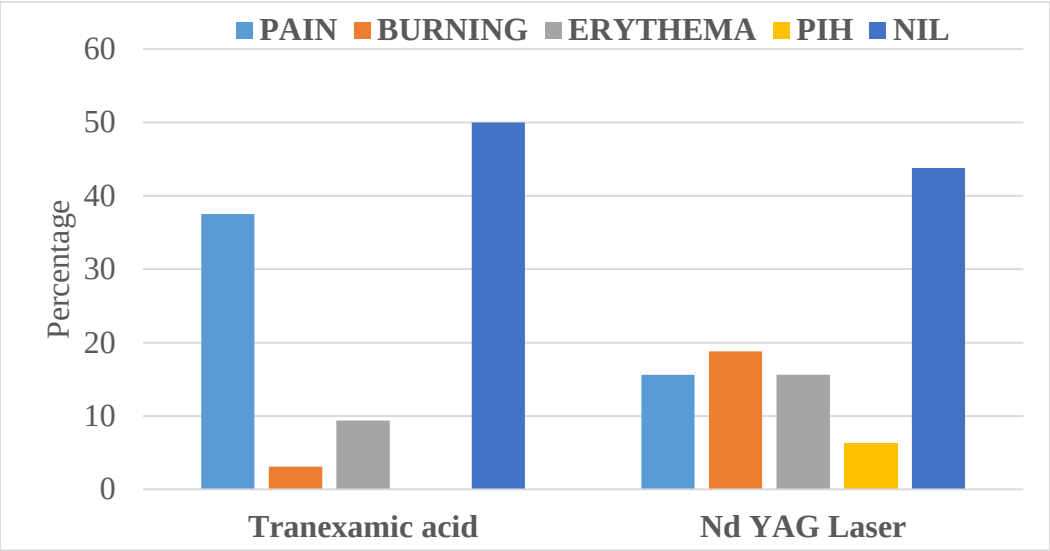


Graph 10:- Graph showing Distribution of subjects according to recurrence

Table 15:- Distribution of subjects according to side effects

	Group		Total
	Tranexamic acid	Nd YAG Laser	
Pain	12	5	17
	37.5%	15.6%	26.6%
Burning	1	6	7
	3.1%	18.8%	10.9%
Erythema	3	5	8
	9.4%	15.6%	12.5%
PIH	0	2	2
	.0%	6.3%	3.1%
Nil	16	14	30
	50.0%	43.8%	46.9%
Total	32	32	64
	100.0%	100.0%	100.0%

P value 0.059, there was no statistically significant difference found between groups with respect to side effects.



Graph 11:- Graph showing Distribution of subjects according to side effects

Table 16:- mean MASI difference in Tranexamic acid group

MASI SCORE	Tranexamic acid	
	Mean	SD
Baseline	15.30	4.76
2 week	14.75	4.63
3week	14.39	4.61
4week	13.28	4.68
P value	**<0.001**	

Among group Tranexamic acid Shows the mean values of difference between MASI at baseline (MASI I) and MASI in final follow up (MASI IV) were analyzed by ANOVA (analysis of variance).The P value is 0.0001. This clearly indicates that there exists a statistical significant.

Table 17:- Multiple comparison with Tranexamic acid group

MASI SCORE	Mean	SD		Mean	SD	P value
Baseline	15.29	4.75	**2 week**	14.7500	4.6344	<0.001
Baseline	15.29	4.75	**3week**	14.3938	4.6132	<0.001
Baseline	15.29	4.75	**4week**	13.2781	4.6799	<0.001

There was a statistically significant difference found between baseline and 2nd week, There was a statistically significant difference found between baseline and 3rd week, There was a statistically significant difference found between baseline and 4th week.

Table 18:- mean MASI difference in Nd YAG Laser group

MASI SCORE	Nd YAG Laser	
	Mean	SD
(BASELINE)	19.26	5.67
2 week	14.88	5.70
4week	10.81	4.68
P value	<0.001	

Among group Nd YAG Laser Shows the mean values of difference between MASI at baseline (MASI I) and MASI in final follow up (MASI IV) were analyzed by ANOVA (analysis of variance).The P value is 0.0001. This clearly indicates that there exists a statistical significant

Table 19:- multiple comparison with Nd YAG Laser group

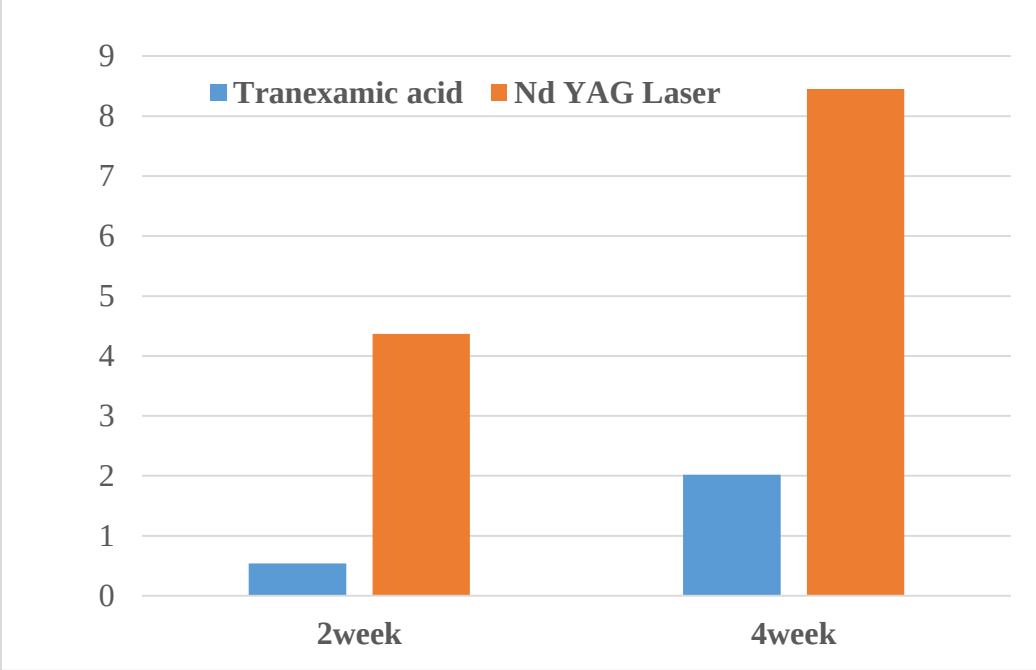
MASI SCORE	Mean	SD		Mean	SD	P value
Baseline	19.26	5.67	**2 week**	14.88	5.70	<0.001
Baseline	19.26	5.67	**4week**	10.81	4.68	<0.001

There was a statistically significant difference found between baseline and 2nd week, there was a statistically significant difference found between baseline and 3rd week, there was a statistically significant difference found between baseline and 4th week.

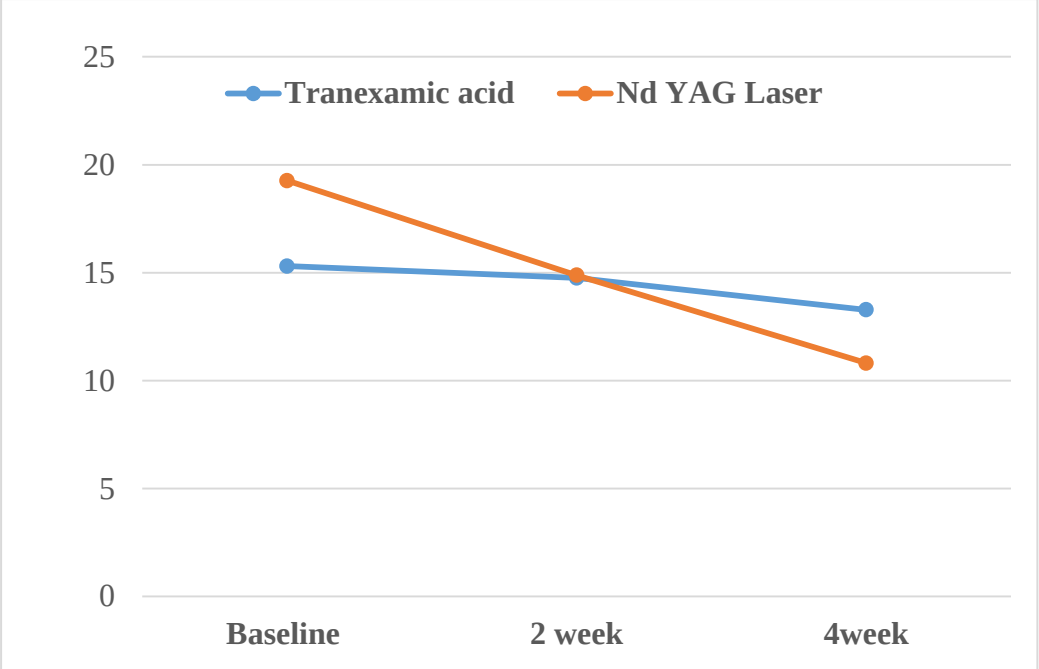
Table 20:- Comparison of reduction in mean MASI between two groups

	Tranexamic acid		Nd YAG Laser		P value
	Mean	SD	Mean	SD	
2week	0.5453	.4788	4.3781	1.9615	<0.001
4week	2.0172	.7848	8.4500	2.9163	<0.001

There was a statistically significant difference found between two groups with respect to mean MASI reduction at 2nd week and 4th week.



Graph 12:- Graph showing comparison of reduction in mean MASI between two groups

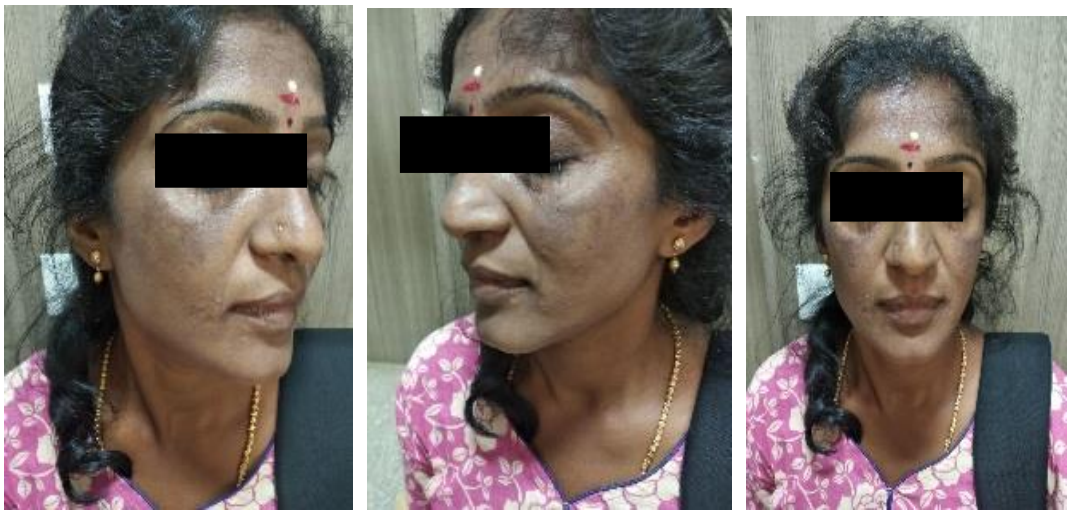


Graph 12:- MASI score at different timelines for both the study groups

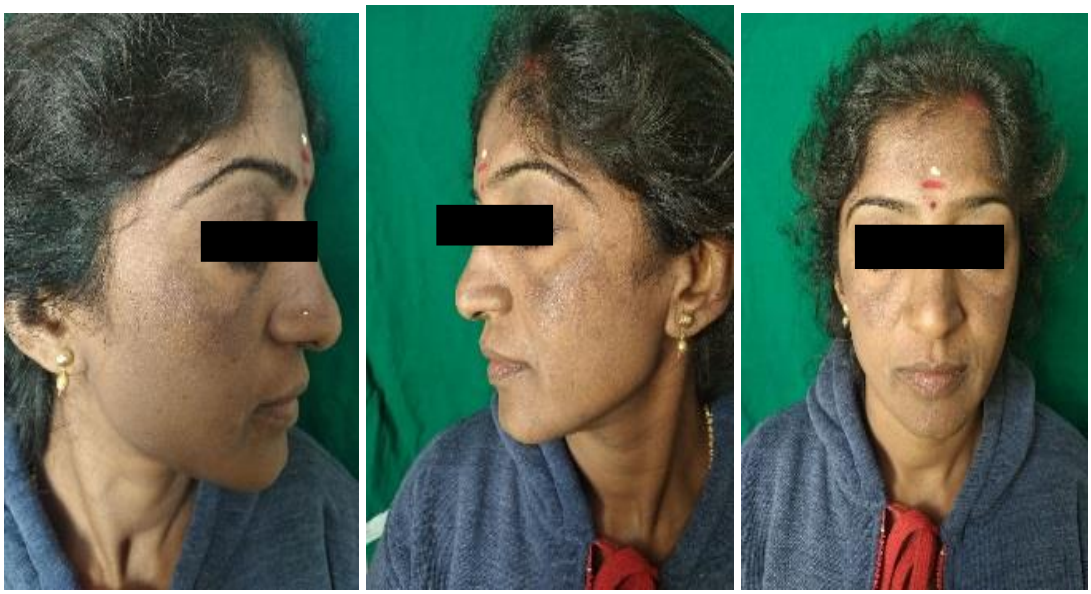
PHOTOGRAPHS

GROUP A- INTRALESIONAL TRANEXEMIC ACID
CASE 1

BASELINE

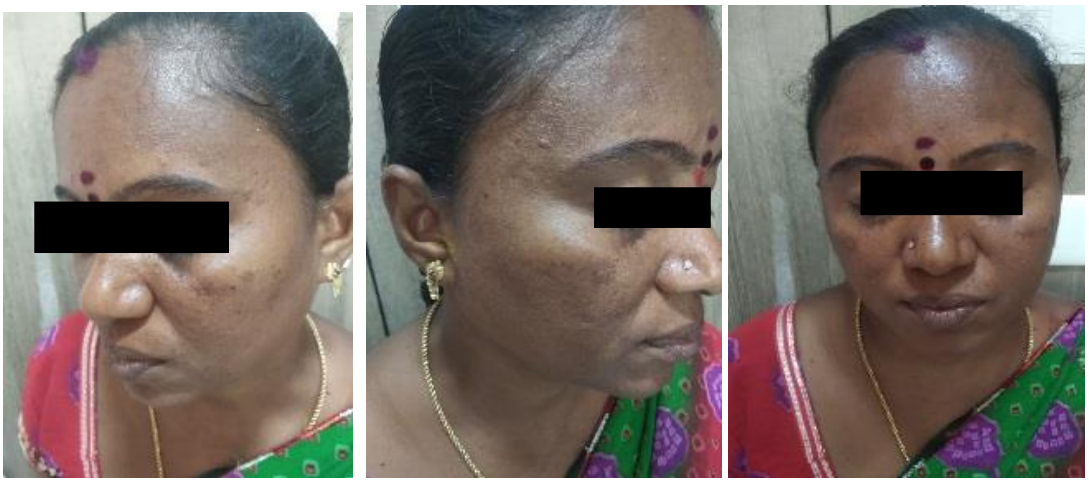


4 WEEKS

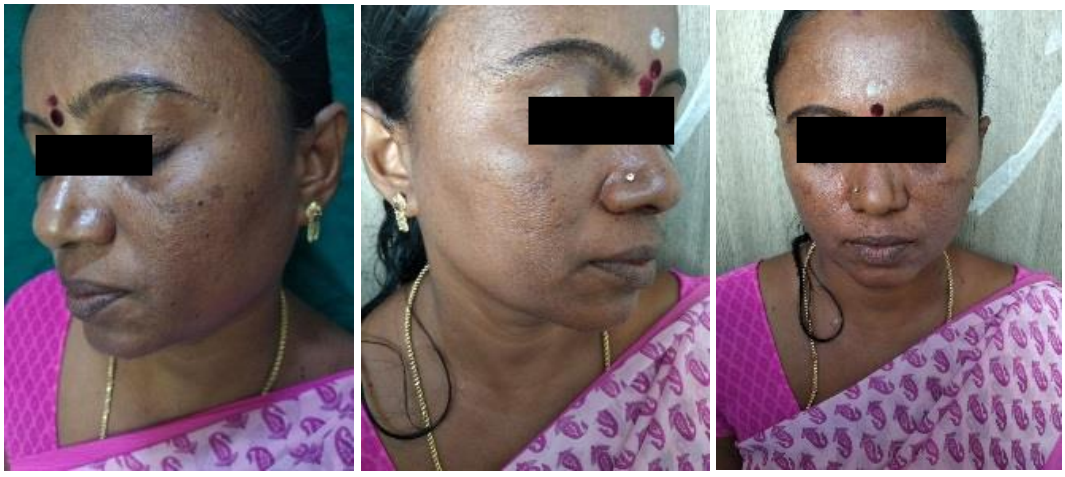


CASE 2

BASELINE

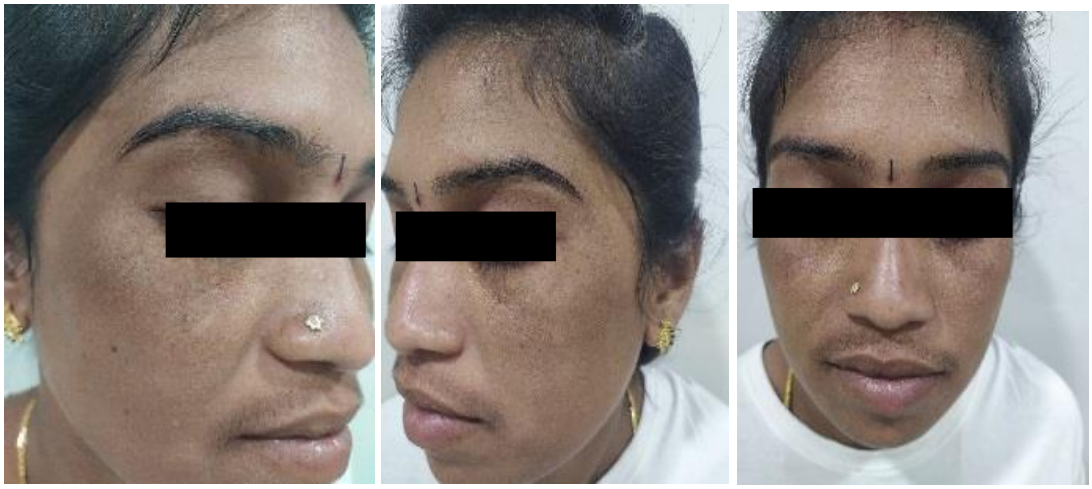


4 WEEKS

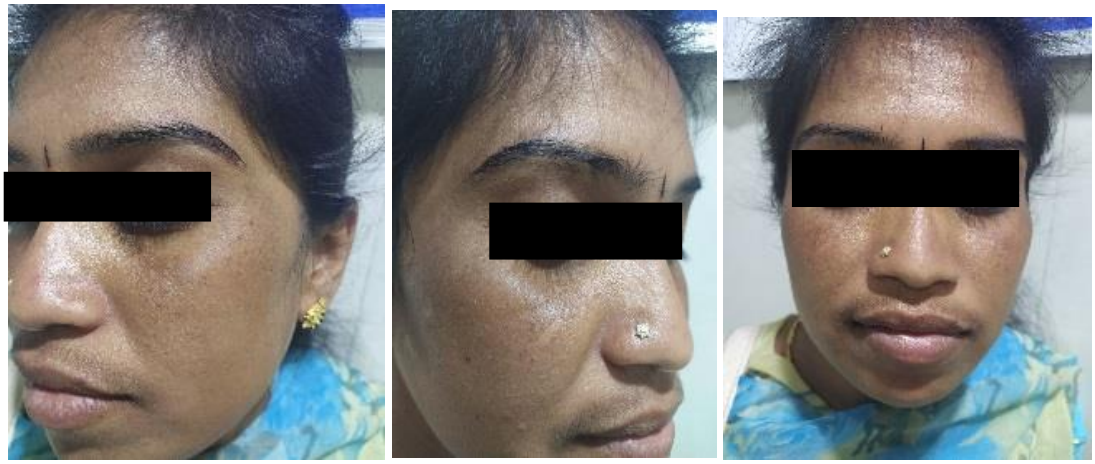


CASE 3

BASELINE

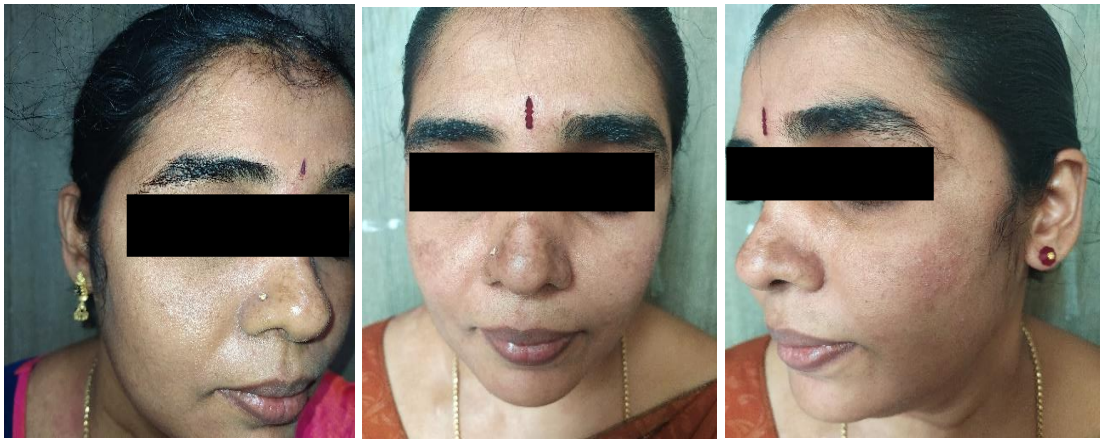


4 WEEKS

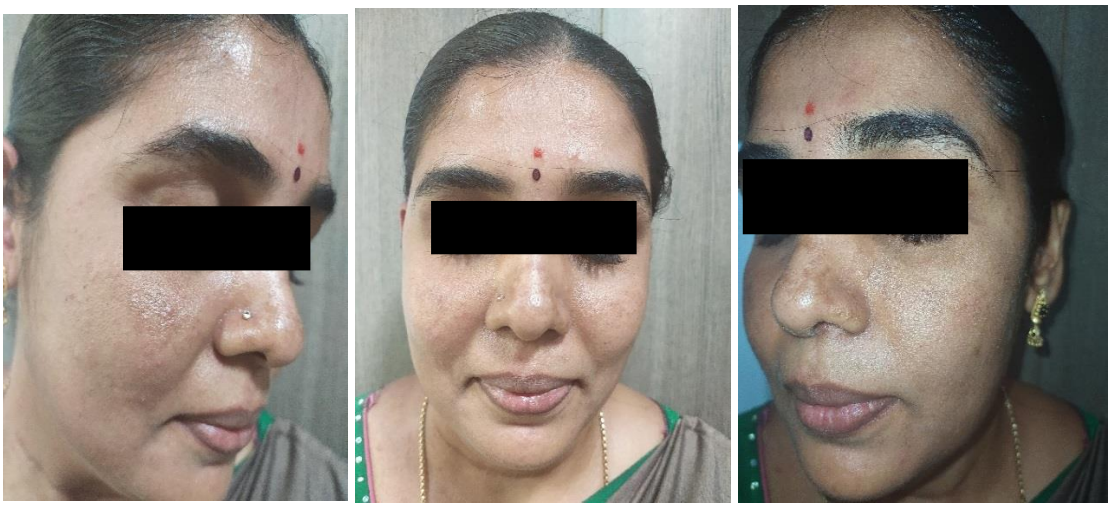


CASE 4

BASELINE



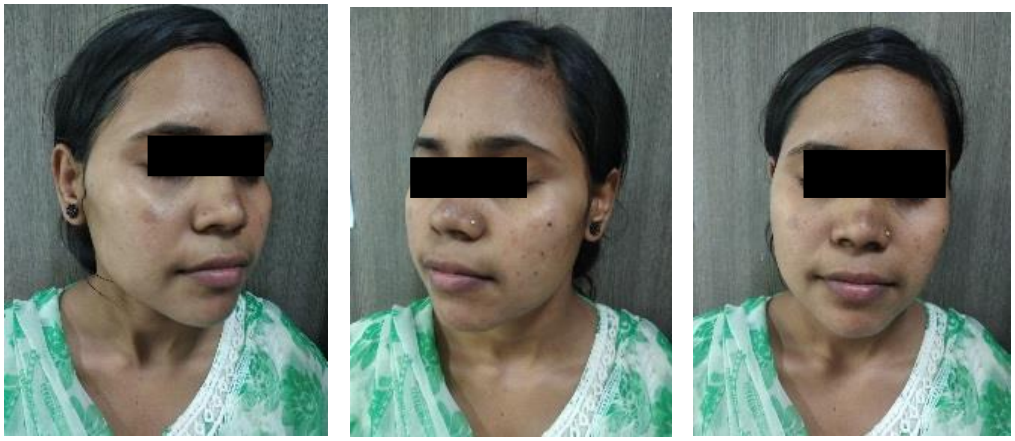
4 WEEKS



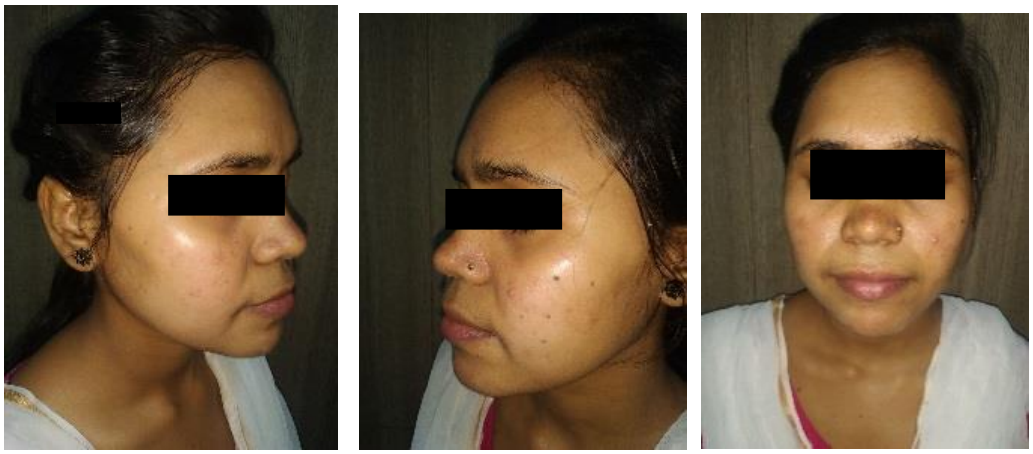
GROUP 2: ND YAG LASER

CASE 1:

BASELINE

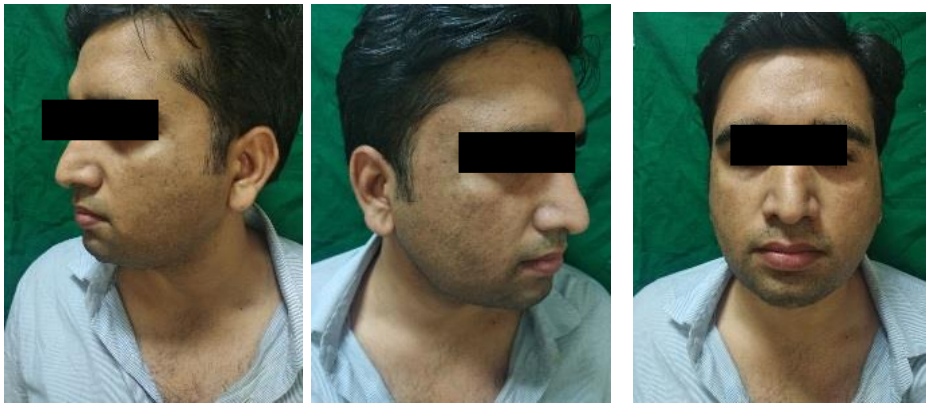


4 WEEKS



CASE 2

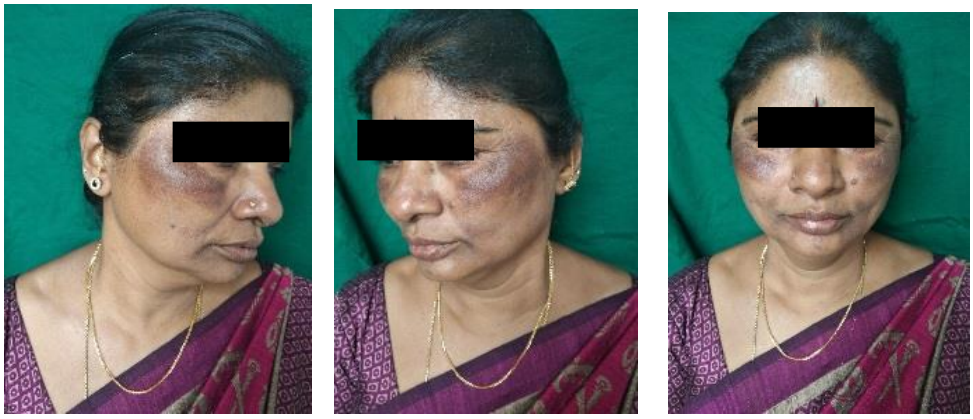
BASELINE



4 WEEKS

CASE 3

BASELINE

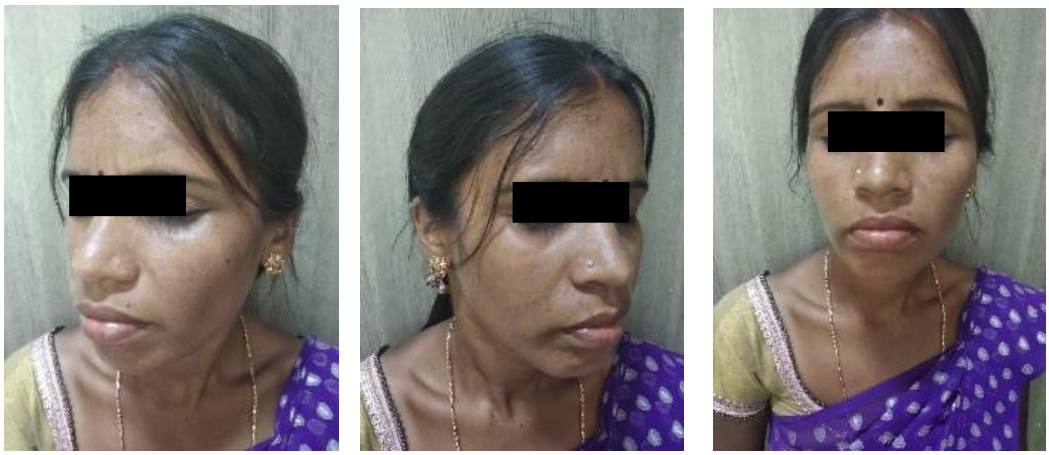


4 WEEKS

CASE 4

BASELINE

4 WEEKS



DISCUSSION

DISCUSSION

Our study was aimed at comparing the efficacy of intralesional tranexamic acid and Nd YAG laser in melasma in 64 patients (32 in each group A and group B)

The mean (SD) age in years of the Tranexamic acid group and Nd YAG laser group was 39.25 (8.41) years and 37.2 (8.64) years respectively. The minimum age of the population was 27 years and maximum was 50 years. The mean (SD) age of the population was 39.96 (8.67) years. In this study most of the subjects belong to the age group of 45-50years 46(31.25%) and next in 30-35years 35(21.1%). Melasma is a disease which is much rarer before puberty and after 50 years. The mean age in our study is comparable with other studies.[21,99,100].

In our study majority 38(59.4%) of the study subjects were females and 26(40.6%) of the subjects were males. Our study showed a female preponderance by 1.4:1. All the studies clearly showed an increased occurrence in females [19, 97, 98]. This higher difference can be attributed to many facts. One factor is the presence of hormonal aggravating factor or application of cosmetics in females compared to males. Also another factor can be due to the increased treatment seeking behaviour of females as melasma is a hyper pigmentation primarily appearing on face.

In our study both the groups had a maximum number of housewives

11(34.4%) in Tranexemic group and 10(31.3%) in Nd YAG laser group. This result is consistent with another study done by Bhattari S et al in Nepal[116]. This can be due to the triggering factor of stress or the more treatment seeking behaviour among females who may be esthetically more apprehensive as melasma affects face.

The mean (SD) duration of disease among the population was 26.14(24.35) months. The mean (SD) of duration of disease was 27.59(24.12) and 24.56(24.49) months among the Tranexemic Acid and Nd YAG laser. In the study maximum subjects 22 (34.4%) had a duration of disease for more than 2 years . Most 11 (34.4%) 16(34%) of the subjects in Tranexemic acid group had a duration of more than 2 years. In the Nd YAG laser group subjects most 11(34.4%) had a duration of more than 2 year. The disease melasma is a chronic condition and high chance of relapse and recurrence is there for the disease. In our study the mean duration of both the group is more than 2 - 3 years. This was similar to other studies (Achar A et al,karn D et al,pawar s et al) where mean duration was above 3 years[19,98,116].

In our study 16(50.0%) of the population in tranexamic acid group had an exposure to sun for 1 - 2 hours. In Nd YAG laser group both 0-2 hrs and 2-4 hrs sun exposure had 10 (31.3%). In the study 26 (40.6%) had an exposure between 0 - 2 hours and 13(20.3%) had an exposure of more than 6 hours. In Orientals, 72.4% patients reported flaring due to sun exposure[99] and another study in India showed exacerbation in 55.1% patients with melasma[19]. Griffiths CE, et al study showed duration of sun exposure was

a precipitating factor in98%of melasma cases[1,18] .The use of sunscreen is successful in preventing the development of melasma and in improving the efficacy of additional topical therapies for melasma.

In the study majority of population in both the groups were having no history of OCP usage in the past. Also most of the populations in both the groups were not in the habit of using cosmetics [24(75%) and 24(75%)]. In about 40 - 50% of the female patients the disease is advanced by pregnancy or by the utilization of oral contraceptive. 8% to 34% of women taking combined hormonal oral contraceptive build up melasma, which was also showed after hormone replacement therapy[34, 119]. Even cosmetics can also play a significant role in flaring up of melasma[56].

The study showed that in both the groups malar type of melasma was present mostly 19(59.4%) and 20(62.5%)]. Also wood's lamp examination showed epidermal pattern mostly 19(59.4%) in tranexamic acid group and 17(53.1%) in ND YAG laser group.

A study by Kumari, et al, who reported that malar pattern was common among Indian melasma patients and constituted about 60% and centrofacial pattern was 40%[115]. Similar results were seen in a study done by Grover C, et al which concluded that 53.3% of Indian patients had malar pattern of melisma and 46.6% had centrofacial[114]. This was also in concordance with a study done by Chan et al, Manjula Jaganathan et al, Sabina et al in which majority of Asian patients had malar

pattern[120,121,122].

Controversial results were also found in some studies. According to the study done among Tunisia patients by Guinot C, et al,76% had centrofacial pattern, 23% malar and 1% mandibular[20]. Arun, et al in a study of 312 patients reported that 55.44% had centrofacial pattern, followed by malar(43.26%) and then mandibular (1.6%)[19]. MMU Khan et al came to the conclusion that 64% of Indian melasma patients had centrofacial type, 24% had malar type and 6% had mandibular type [123]. Similar results were seen with a study by Bansal C, et al, 88.33% patients had centro facial melasma[124].

The mean (SD) baseline score for the tranexamic group and Nd YAG laser was 15.25(4.73) and 19.25(5.67) respectively. The two weeks score mean (SD) for the Tranexemic acid and Nd YAG laser group was 14.75(4.63) and 14.88(5.70) respectively. The four weeks score mean (SD) for the tranexamic acid group and Nd YAG laser was 13.28(4.68) and 10.81(4.68) respectively. Also there was a significance difference between MASI score in the both the groups at both two weeks and four weeks.

The other study comparison is shown down.

A study was done by Patil et al where 180 patients were included in the study. Patients were divided into three groups. Group A selected 60 patients who were given

0.05 mL (4 mg/mL) intradermal TA in each cm^2 melasma using an insulin syringe with a 30-gauge needle after application of topical anesthesia with lidocaine and prilocaine every 15 days. Group B selected 76 patients who were given topical application of 3% TA cream once a day. Group C selected 64 patients who were given topical application of triple combination (hydroquinone 2%, tretinoin 0.025%, fluocinolone acetonide 0.01%) once a day with the application of emollient in the morning. The MASI score at baseline and at 6 months for Groups A, B, and C was 15.4 and 2.2, 15.4 and 6.4, and 15.3 and 5.4, respectively. In this study, Group A showed most percentage improvement in MASI score; Group C was next most improved on MASI score with P value.[(128)]

The study by Xu et al. in 2017 was in accord with the Lee et al., although the results were achieved with microneedling (MN) followed by application of TA solution on diseased areas to facilitate epidermal absorption. This group studied a randomized, self-controlled split face study on 28 women, performed weekly for 12 weeks. The study suggested that more than 25% of improvement was observed in 25 patients who treated with MN plus TA and only 10% was found on the control side of the face which was treated with only 0.5% topical TA.[(129)]

A study done by Parra et al included twenty patients who were treated with 10 weekly sessions of low-fluence 1064-nm QS Nd:YAG laser at 1-week intervals. The modified Melasma Area and Severity Index (mMASI) score was evaluated at baseline; 1 week; and 1, 3, and 6 months after treatment. All patients showed improvement by mMASI scores, range (21%–75%) compared with that at baseline. There were no permanent side effects occurred and the recurrence rate was 81%.[(130)]

A study was done by Fabi et al where 20 patients were included in the study. Patient's face was divided into two halves (split face), and on one half of the face low-fluence Q-switched Nd:YAG laser on one side and the low-fluence QSAL to the other side . Masi scores were calculated after three treatments and each follow-up visit 2, 12, and 24 weeks after the last treatment. Both the laser treated sides showed a significant improvement in MMASI evaluations after two treatments (22% improvement on the QS-Nd:YAG, 17% QSAL) and each follow-up visit 2 (36% QS-Nd:YAG; 44% QSAL), 12 (27% QS-Nd:YAG; and 24% QSAL), and 24 weeks (27% QS-Nd:YAG; and 19% QSAL) after the last treatment, but there was no significant difference was seen between study groups at any visit.[131]

The above results along with the result obtained in our study showed that both the treatment modalities have shown promising results but the Nd YAG laser group has been to shown better reduction in the MASI score .

LIMITATIONS OF THE STUDY-

1. Dropout rate is higher in intradermal tranexamic acid group probably due to fear of repeated injections

CONCLUSION

CONCLUSION

There are umpteen therapeutic options for melasma.

Q switched Nd:YAG laser was better than intralesional Tranexemic acid for the treatment of melasma.

There was a statistically significant reduction in percentage of MASI with both Intralesional Tranexemic Acid and Q switched Nd:YAG laser.

Pain during the injections and recurrences were some of the common side effects associated with Intralesional Tranexemic acids There is no consensus literature on optimum route, dose and timing of treatments with topical tranexamic acid. The efficacy of tranexamic acid is understood from this study but which mode of administration is better was not studied here. Further studies have to be done to assess which mode of administration of tranexamic acid shows better results and which combination therapies works best for melasma in terms of clearance of pigmentation and maintenance of remission.

Q switched Nd:YAG laser is an effective treatment for melasma patients as it showed larger reduction in MASI score, and also lesser chances of recurrences

SUMMARY

SUMMARY

The study was double blinded randomized trial among 64 subjects; 32 in intra lesional tranexamic acid group and 32 in the Nd YAG laser group. Patients with facial melisma belonging to both sexes, within an age group of 18- 50yrs, and willing to undergo treatment and follow up were included in the study. Patients who were on other melasma therapies within last 6 months and having an unrealistic expectation from the treatment were excluded from the study. Both the groups were given instructions for the application of sunscreens at daytime and group A patients received intradermal tranexamic acid injections at concentration of 4mg/ml once weekly for 4 weeks whereas group B patients received ND YAG laser once in two weeks and assessed using Melasma Severity Index (MASI) score at baseline, 2nd week and 4 th week. Also side effects and recurrence were also assessed during the time.

The mean (SD) age in years of the Tranexamic acid group and Nd YAG laser group was 39.25(8.41) years and 37.2(8.64) years respectively. The minimum age of the population was 27 years and maximum was 50 years. The mean (SD) age of the population was 39.96 (8.67) years. In this study most of the subjects belong to the age group of 45-50 years 46(31.25%) and next in 30-35years 35(21.1%).

In our study majority 38(59.4%) of the study subjects were females and 26(40.6%) of the subjects were males. Our study showed a female preponderance by 1.4:1.

The mean (SD) duration of disease among the population was 26.14(24.35) months. The mean (SD) of duration of disease was 27.59(24.12) and 24.56(24.49) months among the Tranexemic Acid and Nd YAG laser. In the study maximum subjects 22 (34.4%) had a duration of disease for more than 2 years.

In our study 16(50.0%) of the population in tranexamic acid group had an exposure to sun for 1 - 2 hours. In Nd YAG laser group both 0-2 hrs and 2-4hrs sun exposure had 10(31.3%). In the study 26 (40.6%) had an exposure between 0 - 2 hours and 13(20.3%) had an exposure of more than 6 hours.

The study showed that in both the groups malar type of melasma was present mostly 19(59.4%) and 20(62.5%)].

The mean (SD) baseline score for the tranexamic group and Nd YAG laser was 15.25(4.73) and 19.25(5.67) respectively. The two weeks score mean (SD) for the Tranexemic acid and Nd YAG laser group was 14.75(4.63) and 14.88(5.70) respectively. The four weeks score mean (SD) for the tranexamic acid group and Nd YAG laser was 13.28(4.68) and 10.81(4.68) respectively.

There is a significance difference between MASI score in intralesional Tranexemic acid and Nd YAG laser 34(53.1%) of the population had some form of side effects after the treatment. Pain were exclusively for the tranexamic acid group. Erythema and burning sensation were the side effects for the Nd YAG laser group.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Khanna N, Rasool S. Facial melanoses: Indianperspective. Indian Journal of Dermatology, Venereology, and Leprology. 2011 Sep 1; 77(5):552.
2. Sanchez NP, Pathak MA, Sato S, Fitzpatrick TB, Sanchez JL, Mihm Jr MC. Melasma:a clinical, light microscopic, ultrastructural, and immunofluorescence study. Journal of the American Academy of Dermatology. 1981 Jun 1;4(6): 698 -710.
3. Sarkar R, Puri P, JainR, Singh A, Desai A. Melasma in men: a clinical, aetiological and histological study. J Eur Acad Dermatology Venereol [Internet]. 2009 Dec15[cited2019 Sep29];24(7):768–72.
4. Sonthalia S. Etiopathogenesis of melasma. Melasma: A Monograph. New Delhi: Jaypee. 2015 Apr 5: 6 -14.
5. Bandyopadhyay D. Topical treatment of melasma. Indian J Dermatol [serial online] 2009 [cited 2019 Oct 28];54:303-9.
6. Victor FC, Gelber J, Rao B. Melasma: A Review. JCutan Med Surg [Internet]. 2004 Mar 5 [cited 2019 Sep 30]; 8(2): 97 –102.
7. Rito C, Pineiro-Maceira J. Reflectance confocal microscopy in the diagnosis of cutaneous melanoma. AnBras Dermatol [Internet]. 2009 Dec [cited 2019 Sep 30]; 84(6): 636–42.
8. Arora P, Garg V, Sonthalia S, Gokhale N, Sarkar R. Melasma update. Indian Dermatol Online J [Internet]. 2014 [cited 2019 Sep30];5(4):426.
9. Taylor SC. Epidemiology of skin diseases in ethnic populations. Dermatologicclinics. 2003Oct;21(4):601-7.

10. Werlinger KD, Guevara IL, González CM, Rincón ET, Caetano R, Haley RW, Pandya AG. Prevalence of self - diagnosed melasma among premenopausal Latino women in Dallas and Fort Worth, Tex. Archives of dermatology. 2007 Mar1;143(3):423-31.
11. Rathore SP, Gupta S, Gupta V. Pattern and prevalence of physiological cutaneous changes in pregnancy: A studyof 2000 antenatal women. Indian Journalof Dermatology, Venereology, and Leprology. 2011 May1; 77(3): 402.
12. Moin A, Jabery Z, Fallah N. Prevalence and awareness of melasma during pregnancy. International journal of dermatology.2006Mar;45(3):285-8.
13. Parthasaradhi A, Al Gufai AF. The pattern of skin diseases in Hail region, Saudi Arabia. Annals of Saudi medicine. 1998 Nov;18(6):558-61.
14. El- Essawi D, Musial JL, Hammad A, Lim HW. A survey of skin disease and skin- related issues in Arab Americans. Journal of the American Academy of Dermatology. 2007 Jun1;56(6):933-8.
15. Hiletework M. Skin diseases seen in Kazanchis healthcenter. Ethiopian medical journal. 1998 Oct;36(4):245 - 54.
16. Walker SL, Shah M, Hubbard VG, Pradhan HM, Ghimire M. Skin disease is common in rural Nepal: results of a point prevalence study. British Journalof Dermatology. 2008 Feb;158(2):334-8.
17. Tzouveka E. Epidemiology and Risk Factors of Melasma. J Pigment Disord[Internet]. 2015 Oct27 [cited 2019 Oct 1];s4(2):1–3.
18. VázquezM, Maldonado H, Benmamán C, Sanchez JL. Melasma in

Men. Int J Dermatol [Internet]. 1988 Jan 1 [cited 2019Oct1];27(1):25–7.

19. Achar A, Rathi SK. Melasma: a clinico-epidemiological study of 312cases.Indian journalof dermatology. 2011 Jul;56(4):380.
20. Guinot C, Cheffai S, Latreille J, Dhaoui MA, Youssef S, Jaber K, Nageotte O, Doss N. Aggravating factors for melasma: a prospective study in 197 Tunisian patients. Journal of the European Academy of Dermatology and Venereology. 2010 Sep;24(9):1060-9.
21. Hexsel D, Lacerda DA, Cavalcante AS, Filho CA, KalilCL,Ayres EL, Azulay-Abulafia L, Weber MB, Serra MS, Lopes NF, Cestari TF. Epidemiology of melasma in Brazilian patients: a multicenter study. International journal of dermatology.2014Apr;53(4):440-4.
22. Handel AC, Lima PB, Tonolli VM, Miot LD, Miot HA. Risk factors for facial melasma in women: a case –control study. British Journal of Dermatology. 2014 Sep; 171(3):588 -94.
23. Ortonne J, Arellano I, Berneburg M, Cestari T, Chan H, Grimes P, et al. A global survey of the role of ultraviolet radiation and hormonal influences in the development of melasma. J Eur Acad Dermatology Venereol [Internet]. 2009 Nov [cited 2019 Sep42.
24. Handel AC, Miot LD, Miot HA. Melasma: a clinical and epidemiological review. Anais brasileiros de dermatologia. 2014 Oct;89(5):771-82.
25. Halder RM, Grimes PE, McLaurin CI, Kress MA, Kenney JJ. Incidence of common dermatoses in a predominantly black dermatologic practice.Cutis.1983Oct;32(4):388-90.

26. Perez M, Luke J, Rossi A. Melasma in Latin Americans. Journal of drugs in dermatology: JDD. 2011 May; 10(5): 517 - 23.

27. Sonthalia S, Sarkar R. Etiopathogenesis of Melasma. MelasmaA Monogr[Internet]. 2015 [cited 2019Oct 23];2(1):6–6.

28. Kang HY, Suzuki I, Lee DJ, Ha J, Reiniche P, AubertJ, Deret S, Zugaj D, Voegel JJ, Ortonne JP. Transcriptional profiling shows altered expression of wnt pathway –and lipid metabolism–related genes as well as melanogenesis -related genes in melasma. Journal of Investigative Dermatology. 2011 Aug1;131(8):1692-700.

29. Lee DJ, Lee J, Ha J, Park KC, OrtonneJP, Kang HY. Defective barrier function in melasma skin. Journal of the European Academy of Dermatology and Venereology. 2012 Dec;26(12):1533-7.

30. Chung BY, Noh TK, Yang SH, Kim IH, Lee MW, Yoon TJ, Chang SE. Gene expression profiling in melasma in Korean women.Dermatology.2014;229(4):333-42.

31. Kim NH, Cheong KA, Lee TR,LeeAY.PDZK1 upregulation in estrogen-related hyperpigmentation in melasma. Journal of InvestigativeDermatology.2012Nov1;132(11):2622-31.

32. JO HY, KIM CK, SUH IB, RYU SW, HAKS, KWON YG, KIM YM. Co-localization of inducible nitric oxide synthase andphosphorylated Akt in the lesional skins of patients with melasma.TheJournalofdermatology.2009Jan;36(1):10-6.

33. Choi TY, Sohn KC, Kim JH, Kim SM, Kim CH, Hwang JS, Lee JH, Kim CD, Yoon TJ. Impact of NAD (P) H: quinone oxidoreductase- 1 on pigmentation. Journal of Investigative Dermatology.

2010Mar1;130(3):784-92.

34. ResnikS. Melasma induced by oral contraceptive drugs. Jama. 1967 Feb 27;199(9):601 -5.
35. Martin ag, Leal–khouri su. Physiologic skin changes associated with pregnancy. International journal of dermatology.1992Jun;31(6):375-8.
36. Hassan I, Kaur I, Sialy R, Dash RJ. Hormonal milieu in the maintenance of melasma in fertile women. The Journal of dermatology.1998Aug;25(8):510-2.
37. Mahmood K, Nadeem M, Aman S, HameedA, Kazmi AH. Role of estrogen, progesterone and prolactin in the etiopathogenesis of melasma in females. Journal of Pakistan Association of Dermatology. 2016 Dec 22; 21(4):241 -7.
38. Costin GE, Hearing VJ. Human skin pigmentation: melanocytes modulate skin color in response to stress. The FASEB journal. 2007 Apr;21(4):976 - 94.
39. BurkhartC. Chloasmain a man due to oral hormone replacement. Skinmed. 2006 Jan1;5(1):46 -7.
40. Lee AY. An updated reviewof melisma pathogenesis. Dermatologica Sinica. 2014 Dec 1; 32(4):233 - 9.
41. Kang HY, Hwang JS, Lee JY, Ahn JH, Kim JY, Lee ES, Kang WH. The dermal stem cell factor and c -kit are over expressed in melasma. British journal of dermatology. 2006 Jun;154(6):1094-9.
42. Abdel-Malek ZA, Suzuki I, Tada A, Im S, Akcali CA. The melanocortin-1 receptor and human pigmentation. Annalsof

the New York Academy of Sciences. 1999 Oct; 885(1): 117 -33.

43. Jang YH, Lee JY, Kang HY, Lee ES, Kim YC. Oestrogen and progesterone receptor expression in melasma: an immunohistochemical analysis. Journal of the European Academy of Dermatology and Venereology. 2010 Nov;24(11):1312-6.
44. Jang YH, Sim JH, Kang HY, Kim YC, Lee ES. The histopathological characteristics of male melasma: Comparison with female melasma and lentigo. Journal of the American Academy of Dermatology.2012Apr1;66(4):642-9.
45. Lieberman R, Moy L. Estrogen receptor expression in melasma: results from facial skin of affected patients. Journal of drugs in dermatology: JDD. 2008 May; 7(5): 463 -5.
46. Jian D, Jiang D, Su J, Chen W, Hu X, Kuang Y, Xie H, Li J, Chen X. Diethylstilbestrol enhances melanogenesis via cAMP- PKA-mediating up- regulation of tyrosinase and MITF in mouse B16 melanoma cells. Steroids. 2011 Nov 1;76(12):1297-304.
47. Kim EH, Kim YC, Lee E- S, Kang HY. The vascular characteristics of melasma. J Dermatol Sci [Internet].2007 May [cited 2019 Oct 3]; 46(2):111–6.
48. Na JI, Choi SY, Yang SH, Choi HR, Kang HY, Park KC. Effect of tranexamic acid on melasma: a clinical trial with histological evaluation. Journal of the European Academy of DermatologyandVenereology.2013Aug;27(8):1035-9.
49. Bak H, Lee HJ, CHANG SE, CHOI JH, Kim MN, Kim BJ. Increased expression of nerve growth factor receptor and neural endopeptidase

in the lesional skin of melasma. Dermatologic Surgery.2009Aug;35(8):1244-50.

50. Cardinali G, Kovacs D, Del Giglio M, Cota C, Aspite N, AmanteaA, Girolomoni G, Picardo M. A kindred withfamilial progressive hyperpigmentation- like disorder: implication of fibroblast-derived growth factors in pigmentation. European Journal of Dermatology. 2009 Sep1;19(5):469-73.
51. Kim JY, Lee TR, Lee AY. Reduced WIF- 1 expression stimulates skin hyperpigmentation in patients with melasma. Journal of Investigative Dermatology. 2013 Jan 1;133(1): 191 - 200.
52. H. Brilliant MU. The mouse p (pink-eyed dilution) and human P genes,oculocutaneous albinismtype 2 (OCA2),and melanosomal pH. Pigment cell research. 2001 Apr; 14(2):86 - 93.
53. LyttonJ. Na+/ Ca2+ exchangers: three mammalian gene families control Ca2+ transport. Biochemical Journal. 2007 Aug29;406(3):365-82.
54. Miot LDB, Miot HA, Silva MG da, Marques MEA. [Physiopathology of melasma]. AnBras Dermatol [Internet]. [cited2019Oct3];84(6):623–35.
55. Prabha N, Mahajan VK, Mehta KS, Chauhan PS, Gupta M. Cosmetic contact sensitivity in patients with melasma: resultsof apilot study. Dermatology research and practice. 2014;2014.
56. DuarteI, CamposLage AC. Frequency of dermatoses associated with cosmetics. Contact dermatitis. 20 07 Apr;56(4):211-3.
57. Pathak MA, Fitzpatrick TB, Kraus EW. Usefulness of retinoic acid in

the treatment of melasma. Journal of the American Academy of Dermatology. 1986 Oct 1;15(4): 894-9.

58. AG P. Guevara IL. Disorders of hyperpigmentation. Dermatol Clin.2000;18:91-8.
59. Pandya A, Berneburg M, Ortonne JP, Picardo M. Guidelines for clinical trials in melasma. British Journal of Dermatology. 2006Dec;156:21-8.
60. Gupta LK, Singhi MK. Wood's lamp. Indian Journal of Dermatology, Venereology, and Leprology. 2004 Mar 1;70(2):131.
61. Sonthalia S, Jha AK, Langar S. Dermoscopy of Melasma. Indian Dermatol Online J [Internet]. 2017 [cited 2019 Oct 3];8(6):525–6.
62. Costa MC, Eljaiek HV, Abraham LS, Azulay- Abulafia L, Ardigo M. In vivo reflectance confocal microscopyin a typical case of melasma. Anais brasileiros de dermatologia. 2012 Oct;87(5):782-4.
63. Kang HY, Bahadoran P. Application of in vivo reflectance confocal microscopy in melasma classification. Journal of the American Academy of Dermatology. 2012 Jul1; 67(1): 157.
64. Kang HY, Bahadoran P, Suzuki I, Zugaj D, Khemis A, PasseronT, Andres P, Ortonne JP. In vivo reflectance confocal microscopy detects pigmentary changes inmelasmaat a cellular level resolution. Experimental dermatology. 2010 Aug;19(8):e228-33.
65. SarkarR, Arora P, Garg VK, Sonthalia S, GokhaleN. Melasma update . Indian Dermatol Online J 2014; 5: 426- 35
66. Taylor S, Westerhof W, Im S, Lim J. Noninvasive techniques for the

evaluation of skin color. Journal of the American AcademyofDermatology.2006May1;54(5):S282-90.

67. Pratchyapruit W, Vashrangsi N, Sindhavananda J, Tagami H. Instrumental analysis of the pattern of improvement and that of recurrence of melasma in Thai females treated with Kligman–Willis triple combination therapy: confirmation by using its two different formulae. Skin Researchand Technology.2011May;17(2):226-33.
68. Pandya AG, Hynan LS, Bhore R, Riley FC, Guevara IL, Grimes P, Nordlund JJ, Rendon M, Taylor S, Gottschalk RW, Agim NG. Reliability assessment and validation ofthe Melasma Area and Severity Index (MASI) and a new modified MASI scoring method. Journal of the American Academy of Dermatology.2011Jan1;64(1):78-83.
69. Majid I, Haq I, Imran S, Keen A, Aziz K, Arif T. Proposing melasma severity index: A new, more practical, office - based scoring system for assessing the severity of melasma. Indian journal of dermatology. 2016 Jan; 61(1):39.
70. Rodrigues M, Ayala- Cortés AS, Rodríguez- Arámbula A, Hynan LS, Pandya AG. Interpretability of the modifiedmelasma area and severity index (mMASI). JAMA dermatology.2016Sep1;152(9):1051-2.
71. Abraham A, Kaimal S. Sunscreens. Indian J Dermatology, Venereol Leprol[Internet]. 2011 [cited 2019Oct 10];77(2):238.
72. Jimbow K, Obata H, Pathak MA, FitzpatrickTB. Mechanism of depigmentation by hydroquinone. Journal of Investigative Dermatology. 1974 Apr 1;62(4):436 - 49.

73. Picardo M, Carrera M. New and experimental treatments of cloasma and other hypermelanoses. DermatologicClinics. 2007Jul1;25(3):353-62.

74. Prignano F, Ortonne JP, Buggiani G, Lotti T. Therapeutical approaches inmelasma. Dermatologic clinics. 2007 Jul 1;25(3):337-42.

75. Barrientos N, Ortiz-Frutos J, Gómez E, Iglesias L. Allergic contact dermatitis from a bleaching cream. Dermatitis. 2001 Mar1;12(1):33-4.

76. Rigopoulos D, Gregoriou S, Katsambas A. Hyperpigmentation andmelasma. Journal of cosmetic dermatology. 2007 Sep;6(3):195-202.

77. Gupta AK, Gover MD, Nouri K, Taylor S. The treatment of melasma: A review of clinical trials. J Am Acad Dermatol [Internet]. 2006 Dec [cited 2019 Oct4];55(6):1048 –65.

78. Gillbro JM, Olsson MJ. The melanogenesis and mechanisms of skin-lightening agents–existing and new approaches. International journal of cosmetic science. 2011 Jun;33(3):210-21.

79. Cestari TF, Hexsel D, Viegas ML, Azulay L, Hassun K, Almeida AR, Rego VR, Mendes AM, Filho JW, Junqueira H. Validation of a melasma quality of life questionnaire for Brazilian Portuguese language: the MelasQoL -BP studyand improvement of QoL of melisma patients after triple combination therapy. British Journal of Dermatology. 2006 Dec;156:13-20.

80. NguyenQH, Bui TP. Azelaic acid: pharmacokinetic and pharmacodynamic properties and its therapeutic role in hyperpigmentary disorders and acne. International journal of

dermatology. 1995 Feb; 34(2):75-84.

81. HalderRM, RichardsGM. Topical agents used in the management of hyperpigmentation. Skin Therapy Lett. 2004 Jun;9(6):1-3.

82. Lynde CB, Kraft JN, Lynde CW. Topical treatments for melasma and post inflammatory hyperpigmentation. Skin TherapyLett.2006Nov;11(9):1-6.

83. Nakagawa M, Kawai K, Kawai K. Contact allergyto kojic acid in skin care products. Contact dermatitis. 1995 Jan;32(1):9-13.

84. Kahn V. Effect of kojic acid on the oxidation of DL -DOPA, norepinephrine, and dopamine by mushroom tyrosinase. Pigmentcellresearch.1995Oct;8(5):234-40.

85. Sarkar R, Arora P, Garg KV. Cosmeceuticals for hyperpigmentation: What is available?.Journal of cutaneous and aesthetic surgery. 2013Jan; 6(1): 4.

86. Draelos ZD. Skin lightening preparations and the hydroquinone controversy. Dermatologic Therapy. 2007 Sep;20(5):308-13.

87. Resnik SS, Resnik BI. Complications of chemicalpeeling. Dermatol Clin [Internet]. 1995 Apr [cited2019Oct 4];13(2):309–12.

88. Khunger N. Standard guidelines of care for chemical peels. Indian Journal of Dermatology, Venereology, and Leprology. 2008 Jan 1; 74(7):5.

89. Savant SS. Superficial and medium depth chemical peeling. Textbook and Atlas of Dermatosurgery and Cosmetology. 1998.

90. Usuki A, Ohashi A, Sato H, Ochiai Y, Ichihashi M, Funasaka Y. The inhibitory effect of glycolic acid and lactic acid on melanin synthesis

in melanoma cells. Experimental dermatology.2003Oct;12:43-50.

91. Calapai G, Gangemi S, Mannucci C, Miniullo PL, Casciaro M, CalapaiF. Systematic reviewof tranexamic acid adverse reactions.JPharmacovigil.2015Aug26;3(04):1-7.

92. Tse TW, Hui E. Tranexamic acid: an impo rtant adjuvant in the treatment of melasma. Journal of cosmetic dermatology. 2013 Mar;12(1):57-66.

93. Poojary S, Minni K. Tranexamic acid in melasma: areview. Pigmentary Disorders. 2015;2(228):2376 - 0427.

94. Kim MS, Bang SH, Kim JH, Shin HJ, Choi JH, Chang SE. Tranexamic acid diminishes laser- induced melanogenesis. Annalsofdermatology.2015Jun1;27(3):250-6.

95. Lee JH, Park JG, Lim SH, Kim JY, Ahn KY, KIM MY, Park YM. Localized intradermal microinjection of tranexamic acid for treatment of melasma in Asian patients: a preliminary clinical trial. Dermatologic surgery. 2006 May; 32(5): 626-31.

96. Ando H, Matsui MS, Ichihashi M. Quasi- drugs developed in Japan for the prevention or treatment of hyperpigmentary disorders. International Journal of Molecular Sciences. 2010 Jun;11(6):2566-75.

97. Wu S, Shi H, Wu H, Yan S, Guo J, Sun Y, Pan L. Treatment of melasmawith oral administration of tranexamic acid. Aesthetic plastic surgery. 2012 Aug 1;36(4): 964-70.

98. Karn D, Kc S, Amatya A, Razouria EA, Timalsina M. Oral tranexamic acid for the treatment of melasma. Kathmandu UniversityMedicalJournal.2012;10(4):40-3.

99. Starner RJ, McClelland L, Abdel-Malek Z, Fricke A, Scott G. PGE2 is a UVR-inducible autocrine factor for human melanocytes that stimulates tyrosinase activation. Experimentaldermatology. 2010Jul;19(7):682-4.

100. Falcone DJ, McCaffrey TA, Haimovitz-Friedman A, Vergilio JA, Nicholson AC. Macrophage and foam cell releaseof matrix- bound growth factors. Role of plasminogen activation. JournalofBiologicalChemistry.1993Jun5;268(16):11951-8.

101. Dashore S, Mishra K. Tranexamic acid in melasma: Why and how?.Indian Journal of Drugs in Dermatology. 2017 Jul1;3(2):61.

102. Aamir S, Naseem R. Oral tranexamic acid in treatment of melasma in Pakistani population: a pilot study. Journal of Pakistan Association of Dermatology. 2016 Dec 2; 24(3): 198 - 203.

103. Li Y, Sun Q, He Z, Fu L, He C, Yan Y. Treatment of melasma with oral administration of compound tranexamic acid: a preliminary clinical trial. Journal of the European Academy of Dermatology and Venereology.2014Mar;28(3):393-4.

104. Padhi T, Pradhan S. Oral tranexamic acid with fluocinolone- based triplecombination cream versus fluocinolone-based triple combination cream alone in melasma: an open labeled randomized comparative trial. Indian journal of dermatology. 2015Sep;60(5):520.

105. Tan AW, Sen P, Chua SH, Goh BK. Oral tranexamic acid lightens refractory melasma. Australasian Journal of Dermatology. 2017Aug;58(3):e105-8.

106. Lee HC, Thng TG, Goh CL. Oral tranexamic acid (TA) in the treatment

of melasma: a retrospective analysis. Journal of the AmericanAcademyofDermatology.2016Aug1;75(2):385- 92.

107. Sonthalia S, Daulatabad D, Sarkar R. Glutathione as a skin whitening agent: Facts, myths, evidence and controversies. Indian Journal of Dermatology, Venereol ogy, and Leprology. 2016 May 1; 82(3):262.

108. Malathi M, Thappa DM. Systemic skin whitening/lightening agents: What is the evidence?.Indian Journal of Dermatology, Venereology, and Leprology. 2013 Nov1; 79(6): 842.

109. Bansal C, Naik H, Kar HK, Chauhan A. A comparison of low fluence 1064nm Q switched Nd:Yag Laser with topical 20% azelaic acid cream and their combination in melasma in Indian patients. J Cutan Aesthet Surg. 2012;5:266-72

110. Moubasher AE1, Youssef EM, Abou-Taleb DA. Q-switched Nd: YAG laser versus trichloroacetic acid peeling in the treatment of melasma among Egyptian patients. American society of Dermatol Surg. 2014Aug;40(8):874-82

111. Wattanakrai P,Mornchan R, Eimpunth S.Low fluence Q Switched Neodymium doped Yttrium Aluminium Garnet 1064 nm laser for treatment of facial melasma in Asians. Dermatol Surg 2010;36:76 – 87

112. Halachimi S,Haedersdal M, Lapidoth M. Melasma and Laser Treatment: An Evidence based analysis. Lasers Med Sci. 2014;29:589-9

113. Tadokoro T, Kobayashi N, Zmudzka BZ, ITO S, Wakamatsu K Yamaguchi Y, et al. UV-induced DNA damage and melanin contentin human skin differing in racial/ ethnic origin. FASEB J [Internet]. 2003 Jun [cited 2019 Oct 2];17(9):1177 – 9.

114. Grover C, Reddu BS. The therapeutic value of glycolic acid peels in dermatology. Indian JDermatol Venereol Leprol 2003;69:148-50.

115. Kumari R, Thappa DM. Comparative study of trichloroacetic acid versus glycolic acid chemical peels in the treatment of melasma. Indian J Dermatol Venereol Leprol 2010;76:447.

116. Bhattarai S, Pradhan K, Sharma S, Rajouria EA. Clinical patterns and epidemiological characteristics of melasma in a tertiary care hospitalof Nepal. Pigment International. 2017 Jan1;4(1):35.

117. Pawar S, Khatu S, Gokhale N. A clinico- epidemiological study of melasma in Pune patients. Pigmentary Disorders. 2015;2(219):2376-0427.

118. Griffiths CE, Finkel LJ, Ditre CM, et al. Topical tretinoin (retinoic acid) improves melasma. A vehicle - controlled, clinical trial. Br J Dermatol. 1993; 129:415 -21

119. Wu IB, Lambert C, Lotti TM, Hercogová J, Sintim- Damoa A, Schwartz RA.Melasma.GItalDermatol Venereol.2012;147:413–418.

120. Chan R, Park KC, Lee MH, Lee ES, Chang SE, Leow YHet al. A randomized controlled trial of the efficacy and safety of fixed triple combination(fluocinolone acetonide0.01%, hydroquinone 4%, tretinoin 0.05%) compared with hydroquinone 4% cream in Asian patients with moderate to severe melasma. Br J Dermatol.2008;159: 697 -703

121. Krupashankar, D. S. et al. “A Cross-Sectional, Multicentric ClinicoEpidemiological Study of Melasma in India.” Dermatology and therapy(2014).

122. Bhattarai, S., Pradhan, K., Sharma, S. and Rajouria, E. (2017). Clinical patterns and epidemiological characteristics of melasma in a

tertiary care hospital of Nepal. Pigment International, 4(1),p.35.

123. MMU Khan, ARS Ahamed. Study of efficacy and safety of triple combination agent (4% hydroquinone, 0.05% tretinoin and 0.05% clobetasol butyrate) in the treatment of melasma. Faridpur Med. Coll. J.2013; 8(1):2225.

124. Bansal C, Naik H, Kar HK, Chauhan A. A comparison of low fluence 1064nm Q-switched Nd: YAG laser with topical 20% Azelaic acid cream and their combination in melasma in Indian patients. J Cutan Aesthet Surg. 2012; 5(4): 266 -7

125. Khuraiya S, Kachhawa D, Chouhan B, Dua M, Rao P. A comparative study of topical 5% tranexamic acid and triple combination therapy for the treatment of melasma in Indian population. Pigment International. 2019 Jan 1; 6(1):18.

126. Pazyar N, Yaghoobi R, Zeynalie M, Vala S. Comparison of the efficacy of intradermal injected tranexamic acid vs hydroquinone cream in the treatment of melasma. Clinical, cosmetic and investigational dermatology.2019; 12: 115.

127. Nasrollahi SA, Nematzadeh MS, Samadi A, Ayatollahi A, Yadangi S, Abels C, Firooz A. Evaluation of the safety an d efficacy of a triple combination cream (hydroquinone, tretinoin, and fluocinolone) for treatment of melasmainMiddle Eastern skin. Clinical, cosmetic and investigational dermatology. 2019;12:437.

128. Patil SS, Deshmukh AR. Comparative study of efficacy of intradermaltranexamic acid versus topical tranexamic acid versus triple combination in melasma. Pigment Int 2019;6:84-95.)

129. Xu Y, Ma R, Juliandri J, Wang X, Xu B, Wang D, et al. Efficacy of functional microarray of microneedles combined with topical tranexamic acid for melasma: A randomized, self-controlled, split-face study. Medicine (Baltimore) 2017;96:e6897]

130. Hofbauer Parra CA, Careta MF, Valente NY, de Sanches Osório NE, Torezan LA. Clinical and Histopathologic Assessment of Facial Melasma After Low-Fluence Q-Switched Neodymium-Doped Yttrium Aluminium Garnet Laser. Dermatol Surg. 2016 Apr;42(4):507-12)

131. (Fabi SG, Friedmann DP, Niwa Massaki AB, Goldman MP. A randomized, split-face clinical trial of low-fluence Q-switched neodymium-doped yttrium aluminum garnet (1,064 nm) laser versus low-fluence Q-switched alexandrite laser (755 nm) for the treatment of facial melasma. Lasers Surg Med. 2014 Sep;46(7):531-)

ANNEXURES

ANNEXURE I

PROFORMA

Name: **Age:** **Sex:** M/F

OP No.: **Education:**

Address: **Occupation:**

Ph No.:

Email id:

C/C:-

HOPI:-

Drug history:-

Past history:- DM/ HTN/ TB/ Epilepsy/ Asthma/ Atopy.

Others –

Family history:- DM/ HTN/ TB/ Epilepsy/ Asthma/ Atopy.

Others –

Personal history:-

Diet – veg/ non-veg/ mixed Appetite –

Sleep – adequate/ disturbed Bowel & Bladder –

Other habits –

Menstrual history:-

Obstetric history:-

Occupational history:-

1. Exposure to sunlight: yes/ no.
2. Duration of exposure:
3. Type of exposure: intermittent/ continuous/ seasonal.
4. Usage of sunscreen: yes/ no.

General physical examination:-

PR = bpm BP = / mmHg

RR = cpm Temperature =

P I C C L E Others –

Systemic examination:-

CVS – RS –

P/A – CNS –

Local examination:-

Skin –

Fitzpatrick skin type:

Hair –

Oral mucosa –

Nails –

Melasma:-

I. *Pattern of involvement –*
   - Centrofacial (cheeks, forehead, upper lip, nose & chin).
   - Malar (cheeks & nose).
   - Mandibular (ramus of mandible).

II. *Type –*
   - Light brown.
   - Ashen/ bluish grey.
   - Dark brown.
   - Ashen grey/ unrecognized.

III. *Wood's lamp examination –*
   - Enhancement seen.
   - No enhancement seen.
   - Patchy enhancement seen.

IV. *Dermatoscopic examination –*
   - Scattered islands of reticular network of light brown or tan color with dark fine granules.
   - Diffuse blotchy brownish reticular pattern with dark brown granules & globules.
   - Greyish brown or greyish black pigmented specks/ arcuate/ star-shaped/ honey-comb/ annular structures.
   - Diffuse reticular pigmentation of dark brown or black irregular blotches with varying surface morphologies along with dark brown granules & globules.

V. Melasma Area & Severity Index (MASI) –

Factors	Forehead (**f**)	Right malar (**rm**)	Left malar (**lm**)	Chin ©
Area				
Darkness				
Homogeneity				
D + **H**				
(**D** + **H**)*A	*0.3	*0.3	*0.3	*0.1
Total				

Area (**A**) = 0-6 Darkness (**D**) = 0-4 Homogeneity (**H**) = 0-4

0 = no involvement

1 = <10%

2 = 10-29%

3 = 30-49%

4 = 50-69%

5 = 70-89%

6 = 90-100%

$$\mathbf{MASI = 0.3(D_f + H_f)A_f + 0.3(D_{rm} + H_{rm})A_{rm} + 0.3(D_{lm} + H_{lm})A_{lm} + 0.1(D_c + H_c)A_c}$$

MASI = + + + =

Investigations:-

CBC:

Hb%= mg/dl ESR= mm/hr AEC= cells/mm^3

RBC= M/mm^3 WBC= T/mm^3 Plt= L/mm^3

RBS= mg/dl FBS= mg/dl PPBS= mg/dl

Urine analysis:

SIDE EFFECTS	1ST SITTING	2ND	3RD
ERYTHEMA			
PHOTOSENSITIVITY			
HERPES LABIALIS			
EROSIONS			
CRUSTS			
BLISTERS			
SCARRING AND OTHERS			

ANNEXURE II

Consent form – A COMPARATIVE STUDY OF TRANEXAMIC ACID MICROINJECTIONS VERSUS ND YAG LASER IN THE TREATMENT OF MELASMA

I, Mr./Mrs./Ms. _____, aged _____ years, S/D/o _____, & a resident of _____ _____ _____, do hereby declare that I am voluntarily giving my consent to participate/ let my son/ daughter to participate in the study of "A COMPARATIVE STUDY OF TRANEXAMIC ACID MICROINJECTIONS VERSUS ND YAG LASER IN THE TREATMENT OF MELASMA".

I have been explained in my own language about the nature of my skin condition, its prognosis, the treatment options available & their respective side effects. I have also been explained to my full satisfaction, in my own language about the procedure involved in the study. I have been explained that my refusal to consent is however not going to affect my / my patient's right to receive treatment from the department.

I do hereby declare that I will provide complete medical history of the disease, allow myself/ my patient to undergo clinical examination & allow collection of necessary clinical material by the treating Doctor.

I also hereby accord consent to be photographed as & when necessary for the purpose of the study. However, these photographs have to be used only for teaching purposes, clinical presentations & publications but not for advertisements or any other commercial purposes.

Name of the declarant / guardian _____

Signature of the declarant / guardian _____

Name of the witness: _____

Signature of the witness: _____

Name & Signature of the investigator: _____

Date: _____ Place: SDUAHER, KOLAR.

ANNEXURE III

PATIENT INFORMATION SHEET

Study title: A COMPARATIVE STUDY OF TRANEXAMIC ACID MICROINJECTIONS VERSUS ND YAG LASER IN THE TREATMENT OF MELASMA

Study site: R.L Jalappa Hospital , Tamaka, Kolar.

Aim: 1) To study the efficacy of Tranexamic acid in the treatment of melasma.

2) To study the efficacy of Nd YAG laser in the treatment of melasma.

3) To compare the therapeutic effectiveness of Nd YAG laser with Tranexamic acid microinjections in melasma.

Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in this study we will collect information(as per proforma) from you. Relevant blood investigations will be carried out if required. This information collected will be used for dissertation and publication only.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. The expenses required for the above investigations will be funded by the study investigator. This study has been reviewed by the Institutional Ethics Committee and you are free to contact the member of the Institutional Ethics Committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are

required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For any further clarification you can contact the study investigator:

Dr. Amulya.Y.S

Mobile no: 8867571423

E-mail id: amulya.sathyanarayana@gmail.com

ANNEXURE IV

KEY TO MASTER CHART

AGE(years)

25-30 1

30-35 2

35-40 3

40-45 4

45-50 5

SEX

MALE 1

FEMALE 2

OCCUPATION

HOUSEWIFE 1

SOFTWARE 2

FARMER 3

LABOURER 4

TAILOR 5

NURSE 6

DRIVER 7

VENDOR 8

TEACHER 9

OCP USAGE

YES 1

NO 2

NA 3

SUN EXPOSURE

0-2HRS 1

2-4 HRS 2

4-6HRS 3

>6 HRS 4

DURATION OF DISEASE

0-6MTS 1

6MTS-1YR 2

1-1.5YRS 3

1.5YRS-2YRS 4

>2HRS 5

TYPES OF MELASMA

CENTROFACIAL 1

MANDIBULAR 2

MALAR 3

MIXED 4

SIDE EFFECTS

PAIN 1

BURNING 2

ERYTHEMA 3

PIH 4

NIL 5

WOODS LAMP EXAMINATION

EPIDERMAL 1

DERMAL 2

MIXED 3

RECURRENCES

YES 1

NO 2

GROUP 1: TRANEXEMIC ACID																
S.NO	**OP NO**	**SEX**	**AGE**	**OCCUPATION**	**DURATION OF DISEASE**	**DURATION OF SUN EXPOSURE**	**OCP USAGE**	**USAGE OF COSMETICS**	**TYPE OF MELASMA**	**WOODS LAMP EXAMINATION**	**MASI SCORE (BASELINE)**	**2 week**	**3week**	**4week**	**RECURRENCES**	**SIDE EFFECTS**
1	317343	2	36	1	1	1	2	1	3	1	14.5	14	13.8	12.1	1	1
2	380556	1	46	3	4	1	3	2	3	1	10.3	10.1	9.9	9	2	1
3	381048	1	49	6	5	1	3	2	1	2	9.5	9.4	9	7.7	2	5
4	326096	2	33	1	1	1	1	1	3	1	8.7	8.5	8.1	7.2	1	1
5	359563	2	50	1	5	2	2	1	3	1	14.1	13.7	13.4	12.5	2	2
6	327610	1	35	9	1	3	3	2	1	3	13.5	13.1	12.5	11.3	2	5
7	316653	2	43	3	5	4	2	2	3	3	16.8	16.3	16	15.4	1	1
8	320032	2	44	1	3	3	3	2	1	1	13.45	11.4	10.4	9.3	2	5
9	683271	2	38	1	2	3	2	2	1	2	14.9	14.2	14	13.2	1	5
10	543251	2	30	1	4	1	2	2	1	3	21.3	19.6	19.4	18.1	2	5
11	782150	2	39	9	5	1	2	1	3	2	14.7	13.9	13.5	11.5	1	5
12	663251	1	55	3	4	4	3	2	1	3	21.3	19.8	19.4	17.8	1	5
13	364321	1	55	3	4	3	2	2	3	1	10.5	10	9	8.1	2	5
14	657230	1	41	4	4	1	3	2	3	3	8.4	8.3	8	7.2	2	5
15	634587	1	37	6	1	1	3	2	3	1	25	24	23.1	22.9	2	1
16	644196	1	29	2	4	2	3	2	3	3	24	23.5	22	21.2	2	5
17	629360	2	32	1	2	1	2	2	3	1	16.8	15.4	15	14.1	2	1
18	612115	2	33	2	1	3	3	3	1	2	7	6.3	5.8	4.8	2	5
19	732250	1	39	9	5	1	2	2	1	1	11.5	11.3	11	10.2	1	1
20	643210	2	35	1	1	1	1	2	3	1	12.4	12.1	11.9	10.3	2	1
21	663630	1	42	3	5	4	3	2	3	1	13.5	13.2	13	12.2	2	3
22	678312	1	42	4	5	4	3	2	3	1	20.3	20	19.7	18.2	1	5
23	605589	2	29	6	1	1	1	1	3	1	9.5	9.1	8.9	7.3	1	1
24	603145	2	30	1	2	1	2	1	1	1	15	14.7	14.5	13.3	2	5
25	663616	1	60	3	5	4	3	2	3	2	17	16.7	17.4	16.4	1	5
26	652524	1	46	3	5	4	3	2	1	1	20	19.7	19.5	18.3	1	5
27	651493	1	31	4	5	4	3	2	1	1	19	18.7	18.4	17.3	2	1
28	648617	2	46	1	1	1	2	2	3	1	18.5	18.2	18	17.1	1	1
29	689723	2	31	2	1	1	2	1	1	2	14.5	14.2	14	13.2	1	3
30	723002	2	32	1	4	1	1	2	3	1	13	12.7	12.5	10.1	2	1
31	699865	1	41	4	4	4	3	2	3	2	23	22.7	22.5	21.2	1	3
32	660527	2	48	3	5	2	2	2	1	1	17.5	17.2	17	16.4	2	5

GROUP 2: ND YAG LASER															
S.NO	OP NO	SEX	AGE	OCCUPATION	DURATION OF DISEASE	DURATION OF SUN EXPOSURE	OCP USAGE	USAGE OF COSMETICS	TYPE OF MELASMA	WOODS LAMP EXAMINATION	MASI SCORE (BASELINE)	2 weeks	4weeks	RECURRENCES	SIDE EFFECTS
1	615493	1	30	2	1	2	3	2	3	1	15.6	13	11.2	2	2
2	648617	2	46	1	4	2	2	1	1	1	20	15.4	11	2	1
3	648775	1	43	3	5	3	3	2	1	2	24	20.1	12.3	1	4
4	613414	1	34	4	2	3	3	2	3	1	17.2	15.3	11.1	2	4
5	620413	2	56	3	5	1	2	2	3	2	20.3	16	13	2	5
6	612115	2	35	9	1	2	1	1	3	3	18.8	13.3	9.8	2	3
7	728487	1	27	2	2	2	2	1	3	3	19.8	17.5	13	2	5
8	604292	2	33	4	5	2	2	2	3	2	12.9	10.3	6.7	1	5
9	730748	2	49	5	2	1	2	2	1	1	28.6	25.5	20	2	5
10	734457	1	44	6	2	2	3	2	1	1	10.6	7.1	5.2	2	3
11	553576	1	49	8	5	2	3	2	3	1	27.4	23.9	19.4	1	2
12	557635	2	49	1	1	2	2	2	3	2	25.4	23.2	16	2	3
13	557635	2	46	1	2	1	2	1	1	3	20.1	17.2	14.5	2	3
14	569002	2	43	4	5	3	2	2	3	1	26.5	23.3	20.1	2	1
15	545965	2	36	6	2	2	2	1	3	1	13	11.2	8.2	2	2
16	544604	2	48	9	4	1	2	2	3	1	20.9	17.2	11.3	1	1
17	547589	2	44	5	2	2	2	2	1	2	15.4	11.2	8.6	2	5
18	547197	2	32	1	4	1	2	1	3	1	18.4	15.4	12.2	1	5
19	506229	1	39	7	5	3	3	2	1	3	19.2	15.3	10.2	1	5
20	541811	2	36	1	5	1	1	1	1	1	30.5	25.4	19.5	2	2
21	738628	1	48	3	5	4	3	2	3	3	24.7	19.5	13.5	2	5
22	543166	2	35	1	2	1	2	2	1	2	15	9.8	7.3	1	5
23	603507	2	42	8	5	3	2	2	3	1	8.9	3.3	2	1	5
24	740540	2	36	1	4	3	2	2	1	1	27	17.5	11	2	5
25	606595	2	39	3	5	4	2	2	3	2	13.7	8.4	5.5	2	3
26	650318	2	46	1	4	1	2	2	3	1	23	13.4	6.5	2	5
27	644241	2	38	8	1	4	2	1	3	3	23.4	15.4	10	2	5
28	616948	1	63	1	2	1	2	2	1	1	16.5	10.5	6.8	1	5
29	613414	1	34	3	5	4	2	2	1	1	19.4	16.9	12.4	2	1
30	620413	2	63	1	2	1	2	2	3	3	14.5	9.2	5.7	1	1
31	695398	2	34	4	1	3	2	2	3	2	9.6	5.4	4.1	2	2
32	696921	1	39	4	2	4	3	2	3	1	16	10.1	7.8	2	2