DISSERTATION ON

AN OBSERVATIONAL STUDY TO COMPARE PROPHYLACTIC AND THERAPEUTIC SURFACTANT ADMINISTRATION IN PRETERM BABIES AND RETINOPATHY OF PREMATURITY

submitted in partial fulfilment of requirements of

M.S. DEGREE

BRANCH –III (OPHTHALMOLOGY)

Reg.No. 221713105

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MADURAI

The Tamilnadu Dr.M.G.R. Medical University

CHENNAI, TAMILNADU

MAY-2020

CERTIFICATE

This is to certify that this dissertation entitled "**AN OBSERVATIONAL STUDY TO COMPARE PROPHYLACTIC VERSUS THERAPEUTIC SURFACTANT ADMINISTRATION IN PRETERM BABIES AND RETINOPATHY OF PREMATURITY"** is a bonafide record of research work done by **Dr.J.S RASIGA THIVYA,** Post Graduate Resident in Department of Ophthalmology, Madurai Medical College, Madurai.

She has submitted this in partial fulfillment of the regulations laid down by The Tamil Nadu Dr. M.G.R. Medical University, for the award of Master of Surgery Degree Branch III (Ophthalmology), under our guidance and supervision during the academic years 2017-2020.

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This is to certify that this dissertation entitled **"AN OBSERVATIONAL STUDY TO COMPARE PROPHYLACTIC VERSUS THERAPEUTIC SURFACTANT ADMINISTRATION IN PRETERM BABIES AND RETINOPATHY OF PREMATURITY"** is a bonafide record of research work done by **Dr. J.S .RASIGA THIVYA,** Post Graduate Resident in Department of Ophthalmology, Madurai Medical College, Madurai.

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DECLARATION

I, **Dr. J.S RASIGA THIVYA** hereby solemnly declare that, this

dissertation **"AN OBSERVATIONAL STUDY TO COMPARE PROPHYLACTIC VERSUS THERAPEUTIC SURFACTANT ADMINISTRATION IN PRETERM BABIES AND RETINOPATHY OF PREMATURITY"** was done by me.

I also declare that this bonafide work / a part of this work was not submitted by me / anyone else, for any award, for Degree / Diploma to any other University / Board either in India / abroad. This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfilment of the rules and regulations for the award of Master of Surgery degree Branch -III (Ophthalmology) to be held in May 2020.

Place: Madurai **Dr. J.S .RASIGA THIVYA**

Date:

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ANTI-PLAGIARISM CERTIFICATE

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ANNEXURES

INTRODUCTION

RETINOPATHY OF PREMATURITY

Retinopathy of prematurity (ROP) is a multifactorial disease of premature babies and has emerged as an important cause of childhood blindness. It is a vasoproliferative disorder of retina occurring principally in new born preterm infants.

Underlying pathological change is retinal neovascularization ; in response to retinal ischemia.ROP can regress spontaneously in early cases but lead to bilateral total retinal detachment and blindness in later stages.

It is an avoidable cause of blindness. With increased survival of preterm infants, ROP has become the leading cause of preventable blindness through out the world.

Its key pathologic feature, local ischemia with subsequent retinal neovasculaization. Is unique in that the vascular disease is found only in infants with incompletely vascularised retinas. The spectrum of ROP ranges from mild cases without visual sequelae to advanced cases with bilateral irreversible blindness.

HISTORY

ROP was first reported by Terry in 1942 in AJO ("American journal of Ophthalmology"). The name"Retrolental fibroplasias" was framed by

Dr.HarryMessenger. Earlier it was thought to be due to the persistence of hyaloid artery behind the lens and the tunica vasculosalentis. This was later disproved by Owens and Owens. They, by analysing a case series of retrolental fibroplasias , found out that the etiology of the disease was not due to the persistent hyaloid system congenitally. They suggested that the pathogenesis would occur postnatally. In 1950, Multicentre randomized clinical trial was conducted by National Cooperative Study which proposed the association of ROP and supplemental oxygen. This Study proved that the reducing the oxygen supplementation in NICU leads to drop in incidence of ROP. But reducing the supplementation of Oxygen led to increased morbidity and mortality among premature infants.

In 1970s, the concentration of oxygen delivered to the babies was individualised, titrated and monitored using arterial blood gas. This helped greatly to decrease ROP incidence and also to increases the survivability of the babies.

In 1980, incidence of ROP had begun to rise as survival rate of the preterm babies started to rise with advancing care facilities in NICU.

INCIDENCE AND PREVALENCE

In India, ROP incidence is between 38 – 51.9 % in low birth weight babies. In India, annual live births is around 26 million, of which

approximately 8.7% are with BW of < 2000 grams. This shows that almost “2 million newborns” are at risk for developing ROP.

“Vision 2020 programme” of World Health Organization's has identified ROP as one of the significant cause of blindness in middle and high income countries.

Incidence of ROP in gestational age of 24-27 weeks is 89 %. As the gestational age increase, ROP incidence decreases.

ROP incidence in birth weight of <750gms is 90%. As the birth weight increases, ROP incidence decreases. ROP can be seen in 80 to 90 % of low birth weight babies, on oxygen therapy given postnataly.

The table here shows ROP incidence and severity in premature babies with birth weight ≤1,251 g

STUDIES	No. of babies	Any STAGEROP (%)	Prethreshold ROP (%)	Threshold ROP (%)
CRYO-ROP STUDY	4,099	66	18	6

LIGHT-ROP STUDY	361	70	14	5
ET-ROP STUDY	6,998	68		

The following is the table showing the severe ROP incidence among premature babies in CRYO-ROP study and ETROP study

STUDIES	Patients	Prethreshold ROP (%)	Plus (%)	Zone I ROP (%)
CRYO-ROP STUDY	2,699	27	17	2
ETROP-ROP STUDY	2,320	37	24	9

RETINAL VASCULOGENESIS:

Normal retinal vasculogenesis

Michaelson suggested retinal capillaries arise by budding ,from pre existent arteries and veins that originate from hyaloids vessels at the optic nerve head. Ashton suggested mesenchyme grows from optic nerve head

through nerve fibre layer to periphery of the retina. On its posterior egde , a chicken –wire meshwork of capillaries develops undergoes absorption and remodeling to produce entire retinal vessels. Vascular endothelial growth factor appears to be a key factor guiding vascular growth. Provis et al demonstrated its expression just anterior to the developing vessels in normal human retina.

The vascular supply of retina consists of:

1. Choroid vessels ->that are underlying the retina.

2. Retinal vessels-> that are serving the inner retina.

Vision begins at around -> 28 weeks of GA and

Visual responses are measurable-> at around 32 weeks of GA.

Normal retinal vascular development begins at the

optic disc-> at about 16weeks of gestation achieved by vasculogenesis and then proceeds to reach

nasal ora serrata by-> 36 weeks of GA and

temporal ora serrata by-> 40 weeks of GA

As the nasal ora serrata is at a shorter distance from disc compared to the temporal ora serrata, retinal vessels reach it first.

Before 28 weeks of GA, outer segments of photoreceptors inactive, so metabolic demand of the retina is quiet less and so need for nutrition is also low. At this time, entire retina is supplied choroidal circulation by process of diffusion as complete development of **choroidal vasculature is much earlier**

i.e about 22 weeks of gestation.

At 28-32 weeks after birth, **vision begins** due to photoreceptor activation then metabolic demand increases and need for more blood supply also follows, but a little change occurs in the choroidal vasculature. As a result of this, **retina needs vascular supply on its own to meet its metabolic demands.**

There are two laminar layers in retinal vasculature,

the primary superficial layer ;

the ganglion cell layer in deeper retina -both are interconnected by fine capillaries.

Development of cells- astrocytes in the nerve fibre region marks the formation of the primary vascular layer in the retina.

Astrocytes are glial cells functions to provide biochemical support to endothelial cells, helps sense physiologic hypoxia and express VEGF.

VEGF (vascular endothelial growth factor) is an important factor in normal vasculognesis and also has its major role in pathological angiogenesis. It creates a chemotactic gradient in extension of retinal angiogenesis to the peripheral ora serrata. From the optic nerve astrocytes emerge and they migrate just ahead of the developing vasculature.

Astrocytes are restricted to the inner layer of retina normally that allows

them to respond to hypoxia of the inner layers by expressing VEGF which is essential to induce the formation of the superficial layer of blood vessels.

Hyperoxia inhibits the formation of new blood vessel ,by down-regulating the "VEGF expression of astrocyte". This down regulation also delays the natural vascular development of retina.

Insulin like growth factor(IGF-1) is another important factor in retinal vascular development. IGF-1 through control of VEGF activation regulates the retinal vascular development.

PHASES OF ROP:

Mechanism of oxygen's effect on immature retina

Primary stage : retinal vasoconstriction and vascular occlusion

Secondary stage : retinal neovascularisation

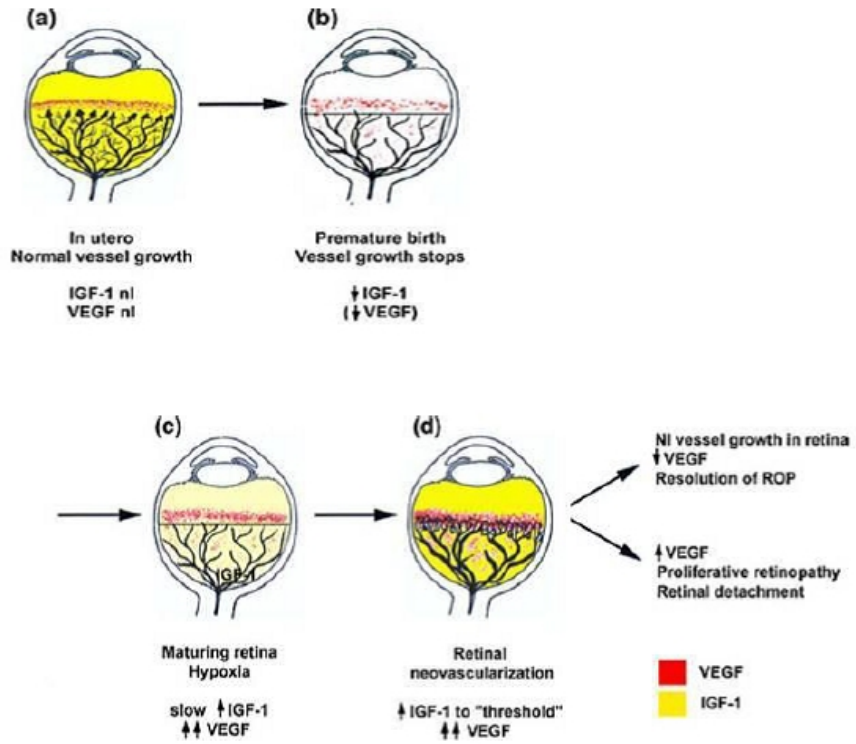
Phase 1: hyperoxia-vasocessation phase.

Occurs from **birth to 30-32 weeks of postmenstrual age**

There is an apparent delay in the regression of hyaloidal circulation. The premature infant's retina become hyperoxic (even in room air) which result in decline in VEGF level, hence vasculogenesis is stopped for a time at the junction of vascular and avascular retina, increasing the risk of development

of ROP.

Hyperoxic state causes VEGF down regulated leading to death of the endothelial cells. Premature infants on exposure to hyperoxia has loss of newly formed capillaries. The fluctuating in blood oxygen levels create varying concentration of VEGF, which is down regulated in hyperoxia and increased during hypoxia.



<u>Phase 2: relative hypoxia - revascularisation phase</u>:

- Occurs at **32-34 weeks of post conceptional age.**

Before 32 weeks of gestation-> as photoreceptors are not fully functional-retina's metabolic demand is low.

After 32 weeks, with a matured retina metabolic demand and oxygen consumption is on rise leading to a state of relative retinal hypoxia.

• The result is an abnormal level of pro-angiogenic growth factors such as erythropoietin and VEGF.

There is a postnatal recovery for IGF-1and on reaching the critical levels,VEGF induces angiogenesis resulting in a, disordered proliferative growth of vessels in the retina if not treated at right time, can later extend into the vitreous causing further complications.

Many multicentral trials have been conducted to analyse the risk factors development of ROP. Most important ones are CRYO-ROP,LIGHT-ROP,ET-ROP.

They analysed the risk factors, progression , prognostic factors of the disease. It also analysed the datas specific to retinal findings of ROP such as onset of disease, Zones or area of the disease involved, stage, progression , presence of plus disease.

Infant specific data- Birth Weight (BW), Gestational Age (GA), gender, race, and multiple births.

Retina specific data - time of disease onset, stage, location, presence of plus disease, rate of progression as well as normal retinal vascularisation patterns

Gestational age ,birth weight, gender, race are compared and analysed.

Decrease in Gestational age and low birth weight was correlated with increase in incidence and severity of ROP.

Race has effect on the incidence of ROP but not on severity.

There is no gender difference in incidence and severity.

Multiple birth has slightly higher risk compared to single birth.

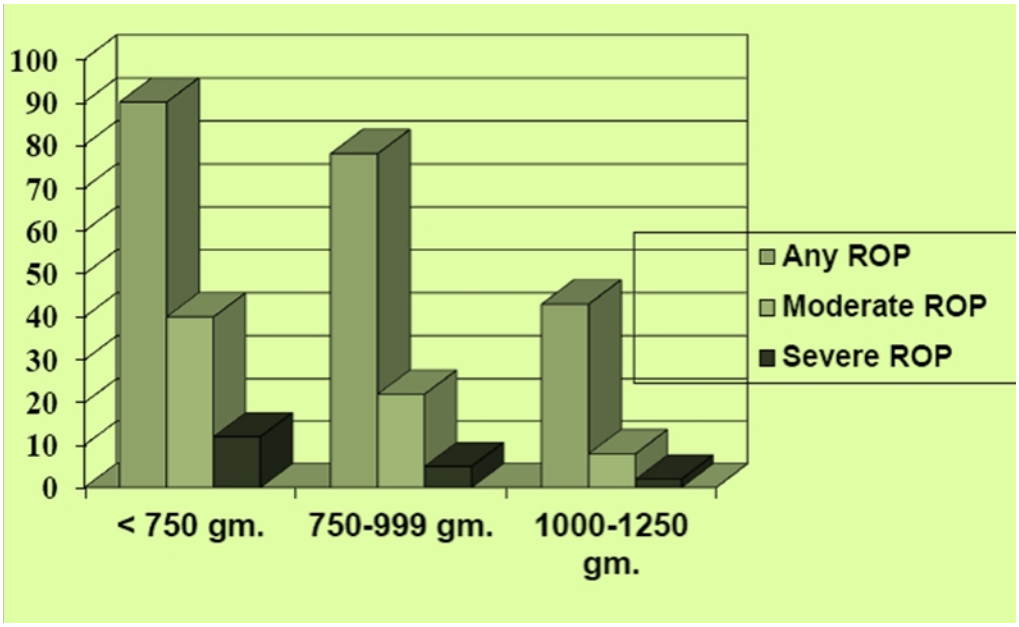
CRYO-ROP study, conducted in 1991here the most dramatic single natural history assessment was made by correlating prethreshold and threshold ROP onset with chronological age (CA) and postmenstrual age (PMA).

Babies has been divided into birth weight quartile as 1,000–1,250 g, 750–1,000 g, and less than 750.

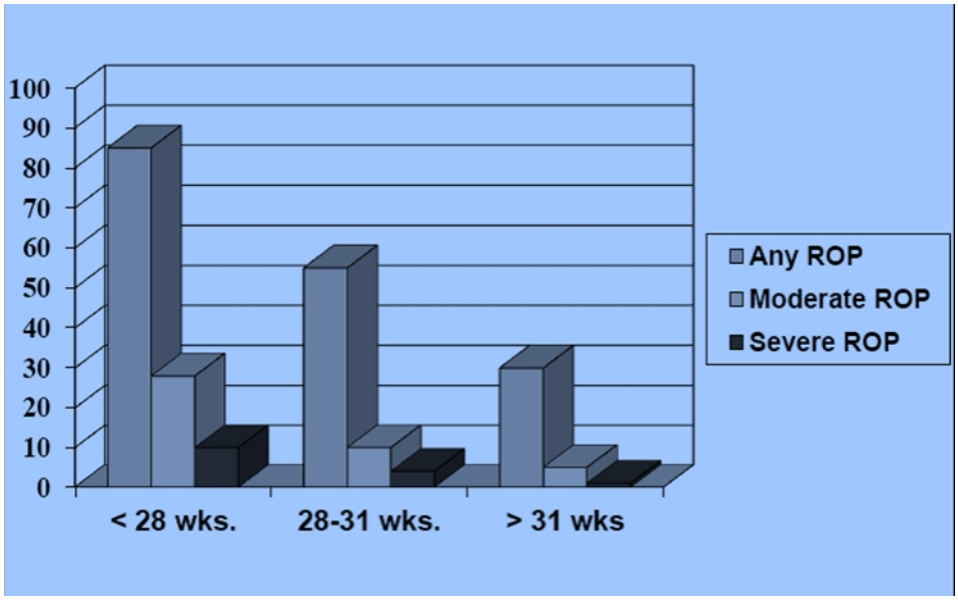
They found that the smallest and most premature babies had longer time duration with the longer period of environmental exposure to develop severe ROP from birth, which has notable role in ROP screening.

STUDIES	MEDIAN ONSET OF PRETHRESHOLD ROP (PMA)
CRYO-ROP study	36.1 weeks
ET-ROP study	36.1weeks

ROP INCIDENCE WITH BIRTH WEIGHT



ROP INCIDENCE WITH GESTATIONAL AGE:



"CRYO-ROP" STUDY:

The major Prognostic indicators are:

1.Status of ROP

2.Zone which is involved

3.Plus disease.

The minor prognostic indicators are:

The circumferential extent of stage 3 disease, and difficult to assessing rate of progression

RISK FACTORS FOR ROP

In general, prematurity, low birth weight, a complex hospital course, and

prolonged supplemental oxygen are the established risk factors for the development of ROP.

ROLE OF OXYGEN

Supplemental oxygen given for a period of weeks, without specific indication, was abundantly documented to be a major cause of ROP earlier but is no longer the predominant factor in cases of ROP seen since the mid-1970s. Now, neonatal advances have resulted in improved survival rates of extremely low-birth-weight children.

The **primary effect of elevated blood oxygen in any retina is 'vasoconstriction'**, which, if sustained, is followed by some degree of vascular closure. Continued oxygen exposure result in ->gradual vasospasm during the next **4–6 hours**, until the vessels are approximately 80% constricted. At this stage, constriction is still **reversible.**

But, if there is **persistence of significantly elevated arterial oxygen partial pressure levels** for an additional period (e.g**., 10–15 hours**), some immature peripheral vessels are **permanently occluded**.

This occlusion progresses as the duration of hyperoxia increases, and local vascular obliteration is complete after 2–3 days of exposure.

In animal models, after removal of the laboratory animal to ambient air, marked endothelial proliferation arises from the residual vascular complexes

adjacent to retinal capillaries ablated during hyperoxia. Nodules of proliferating endothelial cells canalize to form new vessels that not only grow within the retina, but also erupt through the internal limiting membrane to grow on its surface. The initial preretinal neovascular formations are like angioblastic masses with few lumens called “popcorn” , which mature into neovascular malformations that include vessels invested with pericytes.

Although the neovascularization may be extensive, this is generally followed by progressive vascular remodelling and involution. Capillaries regress from areas of higher oxygen concentration and grow toward areas of lower oxygen.

Penn et al. used experimentally alternating periods of high and low oxygen in the rat pup model to produce a more proliferative form of retinopathy.

Pierce and colleagues used hyperoxia and hypoxia in a mouse pup model to demonstrate the correlation of vascular endothelial growth factor (VEGF) protein production with periods of low oxygen, and its disappearance during oxygenation.

ROLE OF GENETIC FACTORS:

In the early 1990s, genetic factors shows its influence in the ROP development, which was the hypothesis put forward and was suggested by the variation noted between different ethnic groups.

This racial variation supports the role of genetic, socioeconomic or dietary factors in ROP development.

Recent clinical and experimental studies with genetic approach in monozygotic twins showed that, there exists a strong genetic predisposition for ROP development.

Studies noted “3 genes (Norrin, Frizzled 4, Lrp5) in Wnt signalling molecular pathways” and these were mutated in some cases of advanced stages of ROP. This explains the progression to severe stage of ROP occurs in some babies even with adequate timely intervention whereas spontaneous regression occurs in other babies with similar ROP.

Numerous other neonatal health factors have been reported to be associated with ROP, including ->

cyanosis, apnea, mechanical ventilation, intraventricular hemorrhages, seizures, transfusions, septicemia, in utero hypoxia, anemia, patent ductus arteriosus, and vitamin E deficiency.

ROP SCREENING AND PREDICTION:

The primary goal of ROP screening is :

- To identify the disease at a stage appropriate for intervention and
- To prevent the following blinding complications.

Treatment window of opportunity - disease must be identified at a stage

when treatment is needed ,but not beyond the stage when treatment would be effective.

ROP screening because it is one of the professional eye examination by Ophthalmologists, there should be “not be any false negatives” unlike other disease screening programs.

Helps in screening the preterm infants who are at risk of developing ROP and diagnosing and treating them at appropriate time.

As ROP can blind a baby, during the crucial period of first 3 months and if necessary measures are taken we can avoid it; a protocol has been recommended for examining the eyes of premature infants during that time span.

The initial eye examination should be performed by 31 weeks postmenstrual age or 4 weeks from birth, whichever is later, in order o to detect prethreshold retinopathy in a timely fashion.

Most risk had passed out whenever full vascularisation had been achieved, and whenever vessels reached the nasal ora serrata without any ROP development prior to that. If the infant reaches 45 weeks of’ gestational age without developing prethreshold ROP or worse, the risk of visual loss from ROP is minimal. The authors caution that recommendations for infants born prior to 24 weeks are by extrapolation.

The current recommendations from the

"American Academies of Ophthalmology and Pediatrics" are that-> children born at 30 weeks or less, or at less than 1500 g, should be screened for ROP.

Specifically those born at a gestational age of 27 weeks or less should have their first exam at 31 weeks and children born from 28 to 32 weeks should have their first exam 4 weeks after birth.

The subsequent examination schedule is determined by findings on the initial examination.

Screening protocol for ROP is given by

"**National Neonatology Forum (NNF)"** and it includes

All preterm neonates born < 34 weeks GA and/or

All preterm neonates with < 1750 grams BW and

Babies born 34-36 weeks gestation or 1750-2000 grams BW along

with the presence of other risk factors for ROP: (cardiorespiratory support,

Respiratory distress syndrome, prolonged oxygen

requirement, fetal haemorrhage, chronic lung disease, sepsis, blood

transfusion, apnoea, intraventricular haemorrhage) are to be screened .

The first ROP screening retinal examination should be done

- not later than 4 weeks of age in babies born ≥ 28 weeks of GA and early
- by 2 to 3 weeks of age in babies born < 28 weeks of GA or < 1200 gram

BW for early identification of AP-ROP screened.

“ROP CLASSIFICATION”

“INTERNATIONAL CLASSIFICATION FOR RETINOPATHY OF PREMATURITY(ICROP)”:

The ICROP guidelines was first published in 1984; updated in 2005 by a committee of 15 ophthalmologists ;the revised ICROP classification highlights

->Description of APROP-an aggressive form

->recognition of Pre plus form of disease

->anatomical definition of Zone 1

It recommends to use 28 D lens with optic disc at the nasal edge.

describes ROP under three aspects: location

extent

severity

by the following terminologies:

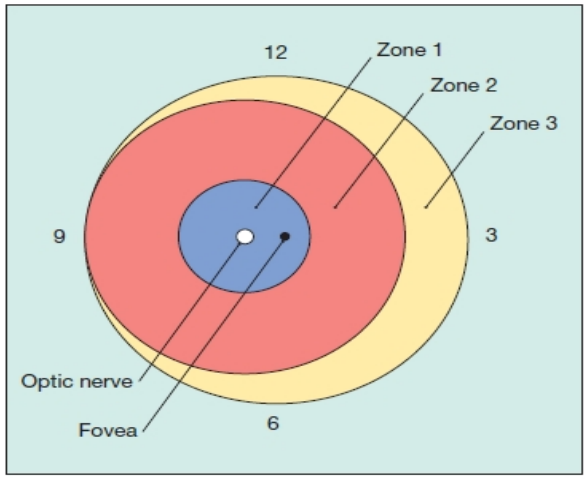
Zones - gives idea about the area of retina which is involved in ROP.

Clock hours - explains the extent of the disease (no longer used).

Plus disease - Characterised by dilated and tortuous retinal vessels in posterior pole.

Anterior segment in plus disease often shows -> distended iris vessels.

ZONES OF RETINOPATHY OF PREMATURITY:



The three zones of ROP are centered on the optic disc:

“Zone I”-uses the optic nerve as the center of a circle, and the radius is defined as twice the distance between the foveola and the centre of optic disc.

“Zone II”- uses as a radius, the distance between the nasal ora serrata in the horizontal meridian and the center of the optic disc.

“ Zone III”- is all of the remaining area is seen in all meridians except at the nasal horizontal meridian.

The ICROP defines **“ five stages of ROP”.**

The process heralds at the junction **between the vascular and avascular retina.**

ROP is described as:

“ Stage 1”- if a narrow white line is present at the junction.

“Stage 2”- is a ridge of activity that shows thickening of this line . In addition to this thickening, there is sometimes a ruddy appearance of a shunt within this

ridge.

“Stage 3”- involves the growth of vessels from the retina toward the vitreous cavity immediately posterior to and contiguous with the ridge

“Stage 4” -is a partial retinal detachment;

subclassified as “4A”- with the macula attached,

and “4B”-with the macula detached.

“Stage 5” -implies a total detachment of the vascularized retina and can be classified further depending on the opening or closure of the anterior and posterior aspects.

STAGE 1 – >“DEMARCATION LINE”

Is the first visible sign of ROP indirect ophthalmoscope.

Appears as a flat , white structure between avascular and vascular retina.

stays within the retinal plane.

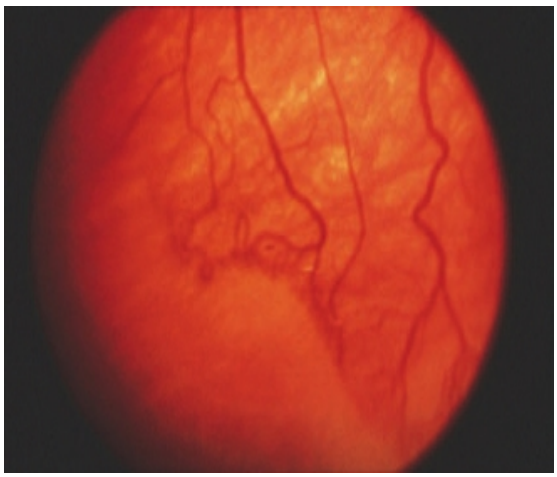
There is an abnormal arcading of vessels leading up to the line.

It either progress to next stage / involutes .

Garner, morphologically describes it as having two relatively distinct zones-

“vanguard”, the anterior zone with spindle-shaped cell mass are considered to be the progenitors of the differentiated vascular endothelium”.

Hyperplasia of these cells ,makes these line ophthalmoscopically visible to us.



STAGE 2– "RIDGE"

The demarcation line in stage 1 ,progresses to ridge by expansion, width and height expands and also extends centripetally within the globe.

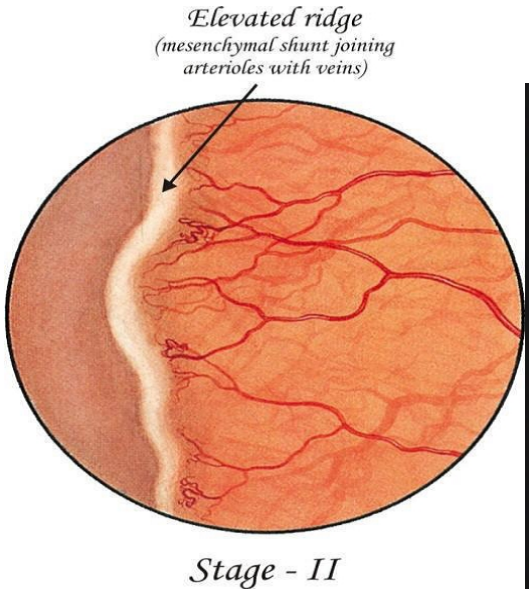
- Colour of the ridge is usually white or pink

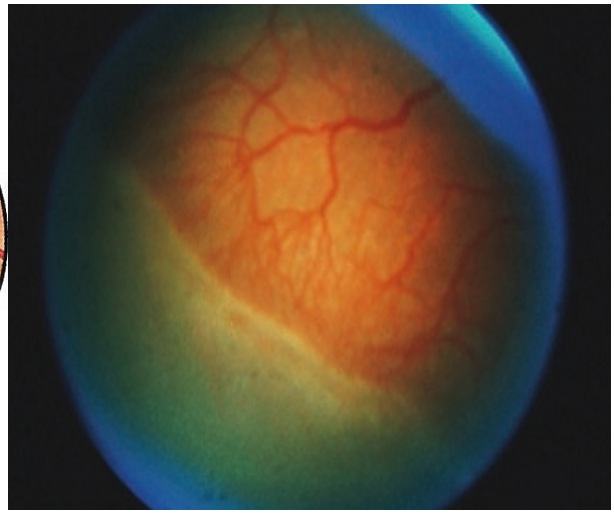
- vessels leave the retinal plane to enter the ridge rarely.

-a small tufts of new vessels called "popcorn vessels"

may be seen posterior to the ridge. They are not attached with the ridge.

- Garner explained these as an actually endothelial cell proliferation with some recogonizable vessel pattern. They leak on fluorescein angiography.





STAGE 3 –> "RIDGE WITH EXTRARETINAL FIBROVASCULAR PROLIFERATION":

-Here, fibrovascular proliferation extends from the ridge towards vitreous extraretinally.

-there is a localised proliferation is localized which is continuous with the posterior aspect of ridge, appearing as a "ragged border".

- three stages have been described, based on proliferation,

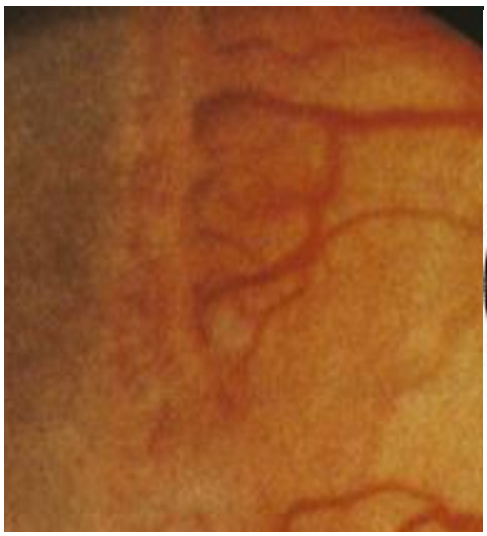
as mild,

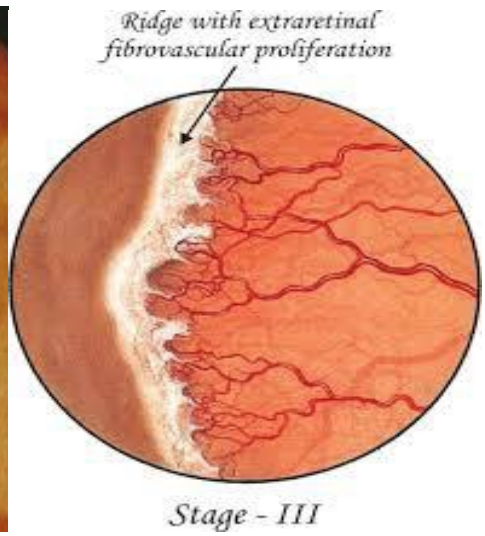
moderate and

severe.

-Foos, by his histopathological description of extraretinal vascularisation gives three types namely ‘placoid’, or ‘polypoid’, or ‘pedunculated’.

-Among these, placoid is the most significant one: as it predisposes to a detached retina.





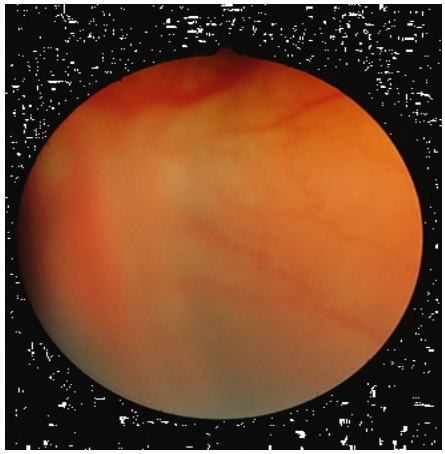
STAGE 4 –“PARTIAL RETINAL DETACHMENT”:

STAGE 4A: “EXTRAFOVEAL RETINAL DETACHMENT”

- Characterized by the presence of tractional detachment at the site of extraretinal fibrovascular proliferation due to the traction caused by vitreous.
- concave retinal detachment ensues.
- involves peripheral part of the retina without affecting macula.

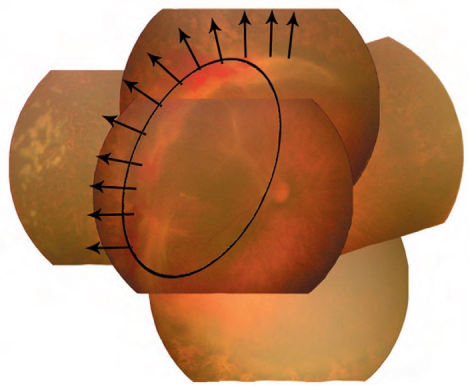
Detachment may be a segmental one or a 360 degree circumferential type. A posterior extension indicates poor prognosis.

- Reattachment may occur spontaneously without functionally affecting macula.



STAGE 4B: “PARTIAL RETINAL DETACHMENT INVOLVING THE FOVEA”

This is a stage with partial retinal detachment involving the macula due to fibrovascular proliferation. “ Macular involvement” gives a poor prognosis.

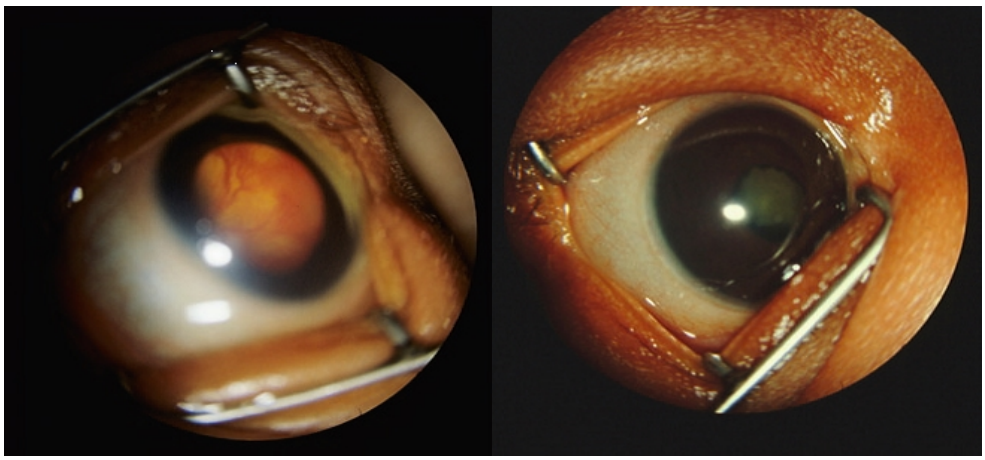


STAGE->“TOTAL RETINAL DETACHMENT”

Total detachment is usually funnel-shaped and based this can be classified as “open” or “closed” and “ anteriorly” or “ posteriorly” .

- First is concave shape and it is open both anteriorly and posteriorly extending upto the disc common type.
- Second one is funnel shaped which is narrow both anteriorly and posteriorly.
- Third one is funnel shaped which opens anteriorly and narrows posteriorly.
- Fourth least type is also funnel shaped which narrows anteriorly but open posteriorly.

These types are diagnosed ultrasonographically.



“PLUS” DISEASE:

Quinn et al coined the term “Retinopathy of prematurity plus” in 1982.

ICROP used the term Plus disease.

Fluctuating o2 levels causes remodelling of vessels in presence of VEGF.

The vascular changes here are characterised by ->

dilated veins and tortuos retinal arterioles in atleast two quadrants at the posterior pole with any stage of ROP.

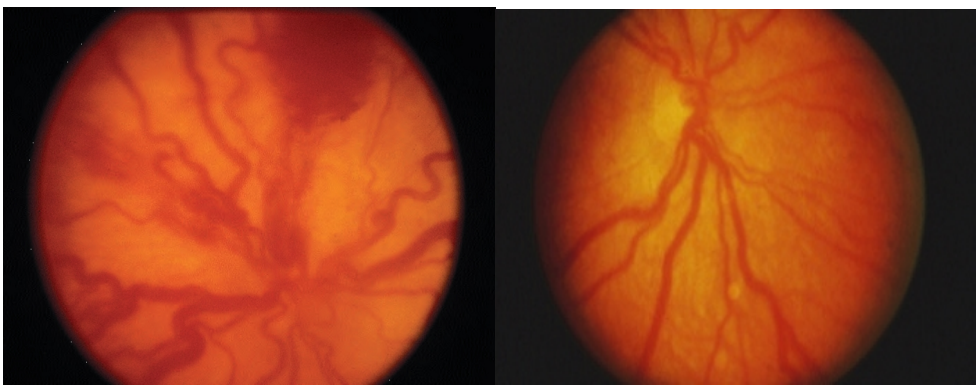
-It is associated with rigid pupil, engorgement of iris and hazy vitreous.

-Improper dilatation of pupil during examination cautions us of Plus disease.

-there is no absolute time in its clinical appearance; though develops between 34 and 38 weeks of gestational age depending upon the gestational age of the infant.

-"anterior segment in plus disease" -> "dilated iris vessels ,represent dilation of an existing tunica vasculosa lentis ,which appears to be a manifestation of a generalized intraocular increased VEGF concentration.

-Indicates poor prognosis.



"PRE PLUS" DISEASE:

By Revised ICROP , "preplus disease" is defined as "vascular abnormalities in the posterior pole ie. more arteriolar tortuosity and more venous dilatation, which are insufficient to meet the diagnosis of plus disease".

-predicts progression to severe ROP

“AGGRESSIVE POSTERIOR” ROP (AP-ROP):

Uncommon, rapidly progressing severe form.

-can occur among the smallest of low birth weight babies.

-located posteriorly with prominent plus disease, deceptively featureless neovasculrization.

-typically seen in zone I ;can also in posterior zone II.

-dilatation and tortuosity out of proportion to peripheral retinopathy.

-Shunting occurs not soley at vascular –avascular junction.

-not progress through classic stages

.

Involution of retinopathy of prematurity

Involution of ROP typically begins after 38 weeks’ postconceptional/postmenstrual age, and may be characterized by a downgrading of staging and/or growth of retinal vessels into a more peripheral zone.

Regressed ROP

The relatively stable state of the eye after retinopathy has run its course is referred as regressed ROP.

Residual changes are classified based on locations:

- Retinal peripheral changes and
- Posterior retinal changes

They are subdivided as follows.

Peripheral changes

Vascular:

Failure to vascularize peripheral retina

Abnormal, nondichotomous branching of retinal vessels

Vascular arcades with circumferential interconnection

Telangiectatic vessels

Retinal:

Pigmentary changes

Vitreoretinal interface changes

Thin retina

Peripheral folds

Vitreous membranes with or without attachment to retina

Lattice-like degeneration

Retinal breaks

Traction or rhegmatogenous retinal detachment

Posterior changes

Vascular:

Vascular tortuosity

Straightening of blood vessels in temporal arcade

Abnormal narrowing or widening in the angle of insertion of major temporal arcade

Retinal:

Pigmentary changes

Distortion and ectopia of macula

Stretching and folding of retina in macular region leading to

periphery

Vitreoretinal interface changes

Vitreous membrane

Dragging of retina over disc

Straightening of blood vessels in temporal arcade

OCULAR COMPLICATIONS IN "REGRESSED ROP":

-Astigmatism

- High myopia, Anisometropia in unilateral ROP. It can be seen in bilateral ROP also.

- Strabismus may develop as a consequence of poor vision(sensory deprivation)

-Amblyopia of the involved eye

-Nystagmus

-Cataract due to fibrovascular proliferation extending till the anterior vitreous phase.

-Glaucoma

-Corneal changes such as band shaped keratopathy, acute hydrops and corneal curvature irregularities .

CICATRICIAL DISEASE:

Occurs in 20% of infants with active ROP and

-ranges from mild to extremely severe form.

-Advanced and more posteriorly located type during resolution will lead on to a worst cicatricial sequelae.

Stage 1 retinal periphery and hazy vitreous base shows pigmentary change

Stage 2: Straightened temporal vascular arcades due to vitreoretinal fibrosis. There is dragging of macula and the optic nerve head.

Stage 3: Severe fibrosis extending to peripheral retina along with contracture causing a falciform retinalfold.

Stage 4: Retrolental fibroplasias ,incomplete ring Anisometropia in unilateral

ROP.

It can be seen in bilateral ROP also. It results in progressive shallowing of the anterior chamber due to forward movement of the iris-lens diaphragm. Subsequently anterior synechiae and secondary angle closure glaucoma is the result.

-anisometropia

-Strabismus due to sensory deprivation.

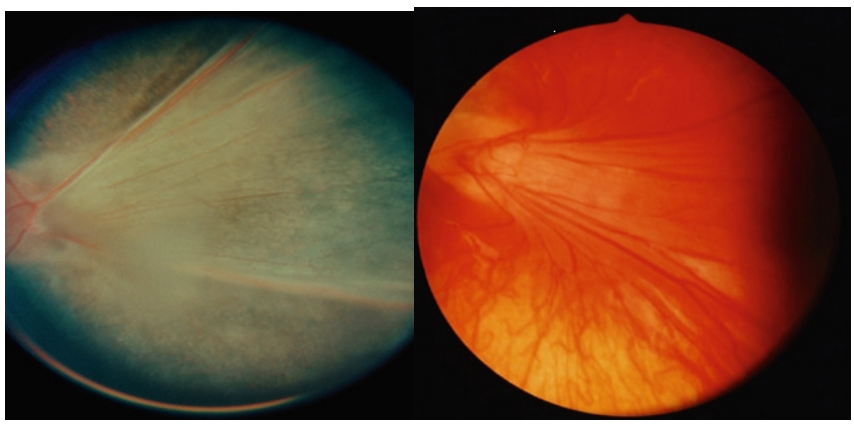
-Amblyopia of the diseased eye

-Nystagmus

-Cataract due to fibrovascular proliferation extending till the anterior vitreous phase.

-Glaucoma

-Corneal changes like band shaped keratopathy, acute hydrops and Irregular corneal curvature



Cicatricial macular changes classification:"MS – Macular score"

"MS-0 Normal

MS-1 Macular ectopia

MS-2 Macular fold

MS-3 Macular detachment

PROTOCOL FOR FOLLOW UP

"Zone I":

Immature retinal vascularisation – >1-2 weeks follow up

Stage 1 or 2 –> 1 week or less follow up

Regressing ROP – >1-2 weeks follow up

"Zone II":

Immature retinal vascularisation – >2-3 weeks follow up

Stage 1 – >2 weeks follow up

Stage 2 – >1 week or less follow up

Regressing ROP – >1-2 weeks follow up

"Zone III":

Stage 1 or 2 – >2-3 weeks follow up

Regressing ROP –> 1-2 weeks follow up

The follow up schedule to be done regularly and the recordings should be documented.

"ET-ROP treatment guidelines" includes,

Type 1 ROP:

It is a new threshold ROP or severe ROP. Treatment for Type 1 ROP is Peripheral retinal laser ablation. It includes

Stage 2 or 3 with plus disease involving zone II

Stage 1, 2, or 3 with plus disease involving Zone I

Stage 3 without plus disease involves Zone I

Type 2 ROP:

It refers to low risk prethreshold ROP or mild ROP. Treatment for type2

ROP is to observe the case for progression. It includes

Stage 3 without plus disease involving Zone II

Stage 1 or 2 without plus disease involving Zone I".

"Aggressive posterior ROP(AP-ROP)" needs ablative laser photocoagulation therapy.

Stage 4(Partial RD) or stage 5 ROP(Total RD)- requires surgical intervention.

DISCONTINUATION OF SCREENING:

We can stop following a baby received laser or VEGF for severe ROP, when it fulfills any one or more of the following criteria ,

- Fully vascularised retina.
- zone III vascularization with no previous zone I or zone II ROP

- Zone III regressing ROP with no abnormal vascular tissue enough to reactivate in zone II or zone III.

  We can decide accordingly.

DIFFERENTIAL DIAGNOSIS:

1. Retinoblastoma

- Its one among the differential diagnosis for stage 5 ROP.

  The history of prematurity and an asymmetrical

  presentation differentiates the two. Ultrasonography clinches the diagnosis.
- USG in retinoblastoma - posterior mass lesion with calcification whereas in ROP- multiple echoeic pattern behind the lens or the retinal detachment .

2. Familial Exudative vitreoretinopathy:

- Clinically can't be differentiated from acute ROP, resembles stage 1 to 3 ROP.
- But by no history of prematurity, its familial.

  History and asymmetrical presentation can be differentiated from ROP. It may present anytime from the birth till first decade.

3. Coat's disease:

- Characterized by abnormal telangiectatic retinal vessels. Features are

Leucocoria initially, followed by retinal edema due to the leaky telangiectatic vessels, yellowish green subretinal fluid and finally exudative detachment.

4. **Persistent hyperplastic primary vitreous (PHPV):**

- Congenital anomaly affecting term infants. unilateral presentation, associated with microcornea. The greyish white membrane seen behind the lens mimics an ROP sequeale.
- In ROP vessels can be seen behind the lens in the fibrovascular

component and there is a posteriorly retinal detachments . In PHPV, no retinal detachment is present ,only a stalk seen extending from the optic disc to the posterior lens surface.

5. **Incontinentia pigmenti:**

- It is a multisystem disorder of females affecting skin, tooth

and nervous system.

- Ocular features are preretinal neovascularisation, non perfusion of

peripheral retina, vitreous haemorrhage and finally tractional retinal detachment. Term born with its characteristic vesiculobullous lesion differentiates it from ROP.

6. **Norrie's disease:**

- X-linked disorder featuring leucocoria, deafness and

mental retardation. Leucocoria manifests at 4-6 weeks of age.

- In ROP manifestation of leucocoria is at a very late stage i.e., stage 5 ROP.

PREVENTION:

Primary prevention is to decrease the incidence of preterm birth and low birth weight babies by which can decrease ROP incidence.

- By giving proper prenatal care, avoiding of illegal drug use help promoting healthy gestation and reducing ROP incidence.

- In 1990 .The "STOP-ROP study" is conducted->a multicentred trial done to eliminate the hypoxic states leading to the formation of new vessels.
  - This trial was done on 694 infants suffering prethreshold ROP. Babies were randomly assigned in two groups. One group maintains Oxygen supplementation saturation levels kept at 96%-99% .Another group at 89%-94% which is a conventional saturation level.
  - There showed a statistical difference between the two groups (41% versus 48%) in the progression of threshold ROP .In the subgroup of babies with prethreshold ROP there was no evidence of plusdisease, a post hoc analysis was done .The result showed a significant reduction (32% versus 46%) in progression to threshold ROP among the supplemental arm.

- Studies were conducted on maintenance of oxygen saturation level between 85%-93% during 2003 To 2006 .it showed a significant decrease in prethreshold ROP and “severe ROP”.
- Recent experiments have shown hyaloid regression on exposure to high quality gross light during late gestation affect the development of the retinal vessels.
- Antioxidants such as vitamin E and D-penicillamines helps in reducing ROP incidence according to certain studies .and the results were controversial

RET CAM II:

Ret cam II is the screening tool used to detect retinopathy of prematurity. A contact retinal camera has to be placed over the cornea using a bridging coupling fluid.

High resolution digital colour photographs obtained with wide field view. As the survival rates of premature babies are on increase, it becomes an useful tool in detecting ROP with ease.

Clarity of images, portability and reliability of findings of made it a easy tool for diagnosis and teaching.

TREATMENT:

- Aim is the maximal structural and functional preservation of neurosensory retina , minimising the complications.

- Peripheral diode laser photocoagulation stands higher than cryotherapy in treating ROP.
- Cryotherapy was the initial mode of treatment since 1972. It is conducted among 291 infants whose weight is less than 1250g who having stage 3 ROP in area posterior to zone III involving 5 clock hours. They were randomized to either cryotherapy or none within 72 hours of diagnosis or observation.
- CRYO-ROP study done for 10 years,

  -among the untreated eyes of threshold disease involving zone II, 62%-had a poor visual outcome

  - among untreated ROP of zone I, 87% -had poor visual outcome.
- Due to significant decrease in unfavourable complications such as retrolental tissue, posterior retinal folds, retinal detachment among the treatment group (i.e.,31% treated versus 51%observed), the "CRYO-ROP study" was stopped earlier at that time. But some 254 preterm babies were followed for fifteen-years even after the study period showed the long-term treatment benefits.
- The study group showed good visual acuity among the treated eyes. (i.e., 64% observed versus 45% treated).
- Indirect laser photocoagulation was not widely used on market during

the CRYO-ROP study period.

- There are certain studies suggesting that laser treated eyes showed better Structural and functional outcomes than cryotherapy treated eyes.
- Later in times, a study "Early Treatment of Retinopathy of Prematurity(ETROP)" was conducted to determine the effect of early treatment in visual outcome.

In ETROP study, "prethreshold ROP" was further subdivided into

type1 ROP and type2 ROP.

In type1 ROP, there was more than 15% chance of getting unfavourable outcomes based on the characteristics of the eyes and infant from the CRYO-ROP.

In type 2 ROP, in there was less than 15% chance of getting unfavourable outcome.

ETROP study suggested ,

Treatment for

type 1 ROP : Peripheral laser photocoagulation ablative treatment and

type 2 ROP : follow up twice weekly upto improvement or upto non progression to high risk state.

End results are: good visual outcome with reduced complications -14.5% in group who were treated early at Prethrehold stage;

And its 19.5% in conventional group where treatment is received at

threshold stage. The results were significant on statistical analysis.

Followup after 6 months showed fewer structural complications, but no significant difference in visual acuity in early treatment group.

But when subgroups are analysed, there is improved visual acuity in zone 1 early treatment group.

BEAT – ROP STUDY:

To assess the effect of bevacizumab in anti neovacularisation activity .

Used Bevacizumab (anti-VEGF antibody) as intravitreal injection, at a dose of 0.625 mg in 0.025 ml.

Administered to 150 infants enrolled in the study who has definite plus disease and assigned randomly for intravitreal bevacizumab or conventional laser.

Bevacizumab-> proved beneficial in eyes showing zone 1 stage 3+ ROP or posterior zone 2 with plus disease.

The sample size of this study was not sufficient to assess the effects of the drug on the developing brain and adverse effects. It also did not address dosage of the drug. Also bevacizumab is not yet FDA approved drug for treating ROP.

Bevacizumab was used in this study only for zone I stage 3+ROP. Detailed informed consent were obtained. Follow up were done weekly after

the treatment until the retina vascularises completely. Follow up period should be longer than for the conventional laser ablation as recurrent stage 3 ROP is more common with anti-VEGF than the laser ablation treatment. Follow up should be assured after bevacizumab treatment especially after the discharge or transfer of the baby from neonatal unit.

CURRENT RECOMMENDED GUIDELINES FOR TREATMENT:

- According to ETROP, type 1 ROP should receive laser ablation of avascular retina within 72 hours of its detection.

  Laser photocoagulation burns should be placed from the oraserrata upto the avascular retina anterior to the ridge for 360 degree. Burns should be grey to grey white with one-half laser burn width space between them.

- Rarely ocular complications can occur such as mispositioned laser burns, cataract, post laser inflammation, to the anterior rotation of lens-iris diaphragm leading to glaucoma secondary, vitreous hemorrhage, and pthisis bulbi very rarely.

- Systemically, infants may develop apnoea, bradycardia and cardiopulmonary arrest during or following the procedure and so the babies should be followed up closely for the same.

- Topically steroids and cycloplegics are applied for a short time after the procedure. First follow up should be within 3-7 days and then it can be

weekly or more frequently.

- Persistent disease or recurrence is treated with additional laser ablation and vitreoretinal surgery must be considered for progressive stage 4 ROP.

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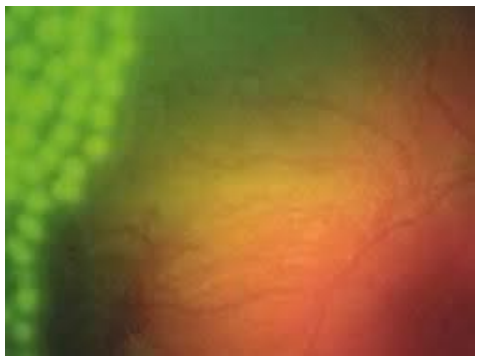


Advantages:

- As cryotherapy is limited to anteriorly located lesions, laser photocoagulation can be used for treating more posteriorly located lesion,
- It promises good structural and functional outcome,
- General anaesthesia is not required.

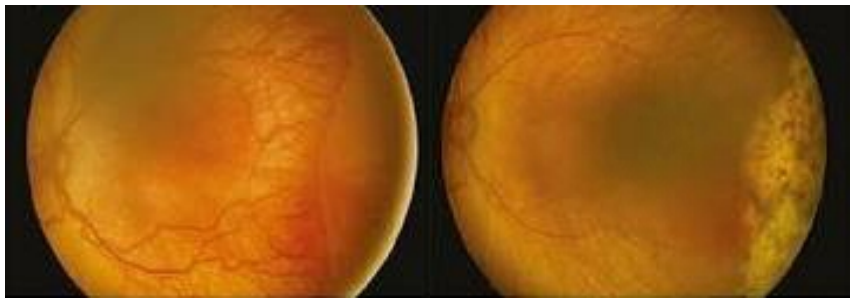
Procedure:

- ❖ Obtain informed written consent from parents or legal guardian before starting the procedure.
- ❖ Nature of the disease, chances of its progression, its complication, long term sequelae, advantage and disadvantage of the treatment should be explained to the parents.
- ❖ Chances of retreatment, surgical intervention, success rate and the importance of long term follow up to be explained.
- ❖ Oral feeds to be stopped at least half an hour prior to the procedure.
- ❖ Presence of neonatologists and anaesthetist during the procedure should be ensured.

- Dilate the pupil adequately.
- If the baby is in incubator , procedure to be done in incubator itself with sloping walls.
- Portable frequency doubled Nd: YAG laser or infra-red diode laser(most commonly used), or anargon laser can be used.
- Laser is delivered by indirect ophthalmoscope. As diode laser penetrates the eyes even with tunica vasculosalentis and vitreous haemorrhage, it is used worldwide than the other lasers for ROP.
- Antibiotic eye drop is applied to the eye to be treated. Paediatric lid speculum is applied. Indentation can be done with scleral depressor.
- + 20 or +28 D aspheric lens can be used for the visualisation of the retina.
- Power of diode laser can be delivered within the range of 300 to 400mw and the duration of laser can be 300 to 400ms.
- Laser settings should be set at the minimum to produce light grey burns.
- Avascular retina is ablated from the ridge to the oraserrata as near confluent burns with one half burn width apart.
- Confluent treatment showed less progression than the dense laser treatment.
- In cases of aggressive ROP, laser spots are delivered to the areas enclosed by flat neovascular loops .
- Pupils can be dilated mechanically if they are rigid or not dilating due to

tunica vasculosalentis.

- ❖ Frequent instillation of carboxymethyl cellulose topically during the procedure provides the clear visualisation of the retina .
- ❖ Topically antibiotic -steroid eye drops to be applied for one week following the procedure to control the inflammation.
- ❖ Some premature infants may develop apnoea during the laser treatment and they immediately need resuscitation and ventilator support.



- Conjunctival congestion, mild chemosis and subconjunctival haemorrhage may occur in some cases of excess scleral indentation.
- Rarely preretinal and vitreous haemorrhage can occur
- Intensive photocoagulation sometime can lead to anterior segment ischemia and also necrosis.

FOLLOW UP:

Follow up should be done after 1week from the procedure.

During the follow up things to be assessed are

- Extent of the plus disease
- Any skip areas
- The status of the ridge and also fibrovascular proliferation if any

- Vitreous organization
- Tunica vasculosa lentis
- whether there is any vitreous haemorrhage

In the of presence of significant plus disease with skip areas during the follow up additional laser can be considered. If Plus disease is seen without skip areas, frequent weekly follow up must be done. Follow up should be continued till the ROP regress.

If no fibrovascular proliferation is seen, follow up is done till 6 months of age. Whereas in the presence of significant fibrovascular proliferation follow up should be at weekly interval to check for the tractional detachment of the retina.

SURGICAL MANAGEMENT FOR RETINAL DETACHMENT:

ETROP study says that 16% of study group with type 1 ROP progresses to retinal detachment in at least one of the eyes.

Retinal detachment can be classified as

- Rhegmatogenous
- Effusive (serous),
- Tractional(fibrovascular)

- Serous RD in stage 4 ROP often resolves spontaneously. Treatment plan either observation or surgical intervention is individualised. Retinal detachment can also occur within 12 weeks of laser treatment. In ETROP study,14% of

eyes developed RD received laser treatment.

- Treatment for progressing stage 4 ROP is the lens-sparing vitrectomy. It releases fibrovascular traction and thus preventing the progression to stage 5 ROP and hence macular structure can be preserved.
- In certain cases, sclera buckling procedure can also be considered for the progressing stage 4 ROP.
- Treatment modalities for stage 5 ROP includes either only scleral buckle or vitrectomy with or without scleral buckle.

Despite of the interventions poor outcomes are seen in the presence of vitreous haze, plus disease and persistent neovascularisation. Scleral buckling has its own disadvantages such as high myopia leading to anisometropia and amblyopia.

OTHERS THERAPIES:

Other treatment modalities are

Anti VEGF,

IGF -1,

- Stem cell therapy,
- Omega 3 poly unsaturated fatty acid,
- Modulators of metabolite signalling growth factors.

VISUAL REHABILITATION:

- As a sequale of ROP infants are more likely to end up with high myopia, squint, amblyopia, heterotropia of macula and glaucoma.
- Aphakic infants or those who underwent scleral buckling requires special rehabilitation for the consequent high refractive error.
- ROP for whom macular vision is affected spectacles should be given to improve the vision and also it act as a protecting agent against ocular trauma.
- ROP infants can have poor vision due to other comorbidities such as hydrocephalus, intraventricular hemorrhage and cerebral visual impairment.

MEDICOLEGAL CONSIDERATIONS:

Screening the premature infants for early diagnosis of ROP and timely treatment has major role in practicing of ophthalmology. There are mainly three things to be aware in ROP care which putforth both the premature baby and the whole healthcare team at risk.

Firstly, ROP risk premature babies typically would have multiple medical consultations for their care. Hence treating ophthalmologists should be aware of the status and the demographical location of the babies they follow

such that screening schedules are not missed.

Secondly, parents of preterm infants are usually overwhelmed and so it is very essential to ensure their compliance for screening, regular follow up and for the treatment.

Thirdly, window for treating the ROP is very short and it may require transferring the critical patient. The whole team of Ophthalmologists, Neonatologists and nurses would be under the litigation when ROP protocols was broken.

Ophthalmologists who is examining and treating the infant for ROP can minimize their exposure to lawsuits by well educating the parents and preserving the documentation of the medical record.

SURFACTANT REPLACEMENT THERAPY

Surfactant deficiency is a major cause of morbidity and mortality in preterm neonates suffering from respiratory failure.

Exogenous surfactant therapy substantially reduces mortality and respiratory morbidity.

Surfactant replacement is done mainly for RDS. But can also be used in other conditions where surfactant is inactivated such as meconium aspiration syndrome, pneumonia, pulmonary hemorrhage, congenital diaphragmatic hernia and acute respiratory distress syndrome.

DESCRIPTION

Endogenous surfactant is a biochemical compound comprising of phospholipids, neutral lipids and proteins forming a layer between terminal airways and alveolar gas.

Klaus and collegues isolated alveolar surfactant from bovine lungs, extracted phospholipid having surface active behaviour. Gluck et al measured lecithin –sphingomyelin ratio in amniotic fluid from surfactant of fetal lung.

Surfactant is secreted by type II pnemocyte. By reducing surface tension ,it reduces lung collapse during end exhaltation. Premature infants have lungs that are surfactant deficient.

Its secondary function is to enhance macrophage activity, mucociliary clearance and reduce inflammation. Lung maturity correlates more than gestational age for RDS.

Exogenous lung surfactant –either natural or synthetic.

Natural surfactant-from animal sources like bovine or porcine.

Surfactant is administered by trained personnel in:

1 Delivery room

2 ICU

3 Newborn nursery (if awaiting external transport to

ICU)

4 Institutions that have the ability to perform neonatal

resuscitation and stabilization procedures.

INDICATIONS

1. Prophylactic administration may be indicated in:

a. Premature infants at high risk of developing RDS secondary to surfactant deficiency (eg 32 weeks or low birth weight

b. Infants in whom there is laboratory evidence of surfactant deficiency such as lecithin/ sphingomyelin ratio 2:1

2. Rescue or therapeutic administration may be indicated in preterm or full-term infants who are suspected of having surfactant deficiency by inactivation

and who require endotracheal intubation and mechanical ventilation secondary to respiratory failure and who require an FIO2 and Clinical and radiographic evidence of neonatal

3 Used as a vehicle to deliver drugs such as antibiotics, anti-inflammatory agents, and bronchodilators.

4 Postoperative development of ARDS following cardiac surgery. The use of exogenous surfactant reduces time on positive-pressure ventilation and reduces the ICU and hospital stay.

5 Treatment of severe respiratory syncytial virus induced respiratory failure.

In RDS, surfactant can be administered either prophylactically or as rescue therapy.

1. **Prophylactic surfactant**: administered within 15- 30 min of birth, irrespective of the presence of symptoms of RDS.

   Its given in preterm neonates <28weeks of gestation, if no or incomplete antenatal steroids to mother or if requiring intubation and mechanical ventilation at birth.

   Administrating surfactant to a previously unventilated or minimally ventilated lung will diminish acute lung injury. Acute lung injury results in alveolar capillary damage, leakage of proteinaceous fluid into the alveolar space and release of inflammatory mediators, resulting in decreased response to surfactant replacement.

2. **Early rescue**: administered in preterm neonates with RDS within 2 hours of birth.

   Early administration of surfactant is advantageous due to the presence of lung fluid which helps in uniform distribution of the surfactant. It also ensures that surfactant is administered before widespread atelectasis develops in the lungs.

3. **Late rescue:** Surfactant is administered after 2 hours. It is done usually in outborn neonates who are transported late to referral centers.

INTRATRACHEAL SUSPENSIONS

Lucinactant is the first FDA for use to treat neonatal RDS. When compared in clinical trials, lucinactant, was found to have similar rates of mortality and morbidity as did beractant and poractant alfa.

Surfactant B is a major component of animal derived surfactants (beractant, calfactant, and poractant alfa) .

SP-B has been found to reduce surface tension to a greater extent than surfactant protein-C (SP-C).

Congenital absence of SP-B is lethal. SP-C deficiency per se is not associated with respiratory failure. Older generation Synthetic preparations of older generations does not contain SP-B like peptides. So animal derived surfactants, are used universally which has variable amount of SP-B protein.

Lucinactant has KL4 protein which mimick SP-B.

Natural exogenous surfactant are on increasing use than lab prepared synthetic surfactant. Natural surfactants are better in lowering of alveolar surface tension and good adsorbing capacity.

It also showed lower oxygen requirement, lower risks of pneumothorax,

bronchopulmonary dysplasia (BPD), and death in controlled trials.

Synthetic preparations may have better quality control than natural surfactants, due to the batch-to-batch variations in the later one.

Natural surfactants are purified by extraction removing hydrophilic proteins.

The special caution in using natural surfactant is transmission of Prion diseases.

Commonly used surfactant preparations

Natural Minced lung 1. Beractant (Survanta)Extracts

2. Poractant alfa (Curosurf)

3. Surfactant TA (Surfacten)

Lung lavage 1. Bovine Lipid Extract Surfactant extracts (BLES)

2. Calfactant (Infasurf)

3. SF-RI1 (Alveofact)

Newer synthetic (protein analogues

New synthetic second generation

1. Lucinactant (Surfaxin)- SPB analogues, Sinapultide
2. rSP-C surfactant(Venticute)-SPanalogues, Lusupultide

Third generation CHF 5633 (SP-B and SP-C enriched synthetic surfactant)

DOSAGE

Term neonates ->usually have a surfactant storage reserve of approx 100 mg/kg, Preterm neonates ->have an estimated reserve only 4–5 mg/kg at birth.

Exogenous surfactant therapy is needed to increase the reserve until its tkan over by endogenous surfactant. Thus a preterm neonate wih RDS needs the 100mg/kg for proper lung function.

High dose poractant is superior than low dose poractant and beractant in reducing mortality according to studies.

USE

Surfactant therapy, on improving cardiorespiratory stability and oxygenation, should other reduce non-pulmonary complications of prematurity such as ->

intra- ventricular hemorrhage (IVH),

necrotising enterocolitis and

retinopathy of prematurity (ROP).

As described earlier, Surfactant can be given as ->

Prophylactic therapy - at or within 30 minutes of birth to those infants at risk of developing RDS, can be given even before the infant has breathed or received positive pressure ventilation) or as Rescue therapy -given only when the diagnosis of severe RDSIS made, usually at 3-6 hours after birth.

The advantages of prophylactic over rescue therapy ->are that

-> For aerating lung and removing excess lung fluid,

- >For equal distribution of the given surfactant, and

-> For reducing barotrauma and thus leakage of inhibitor proteins.

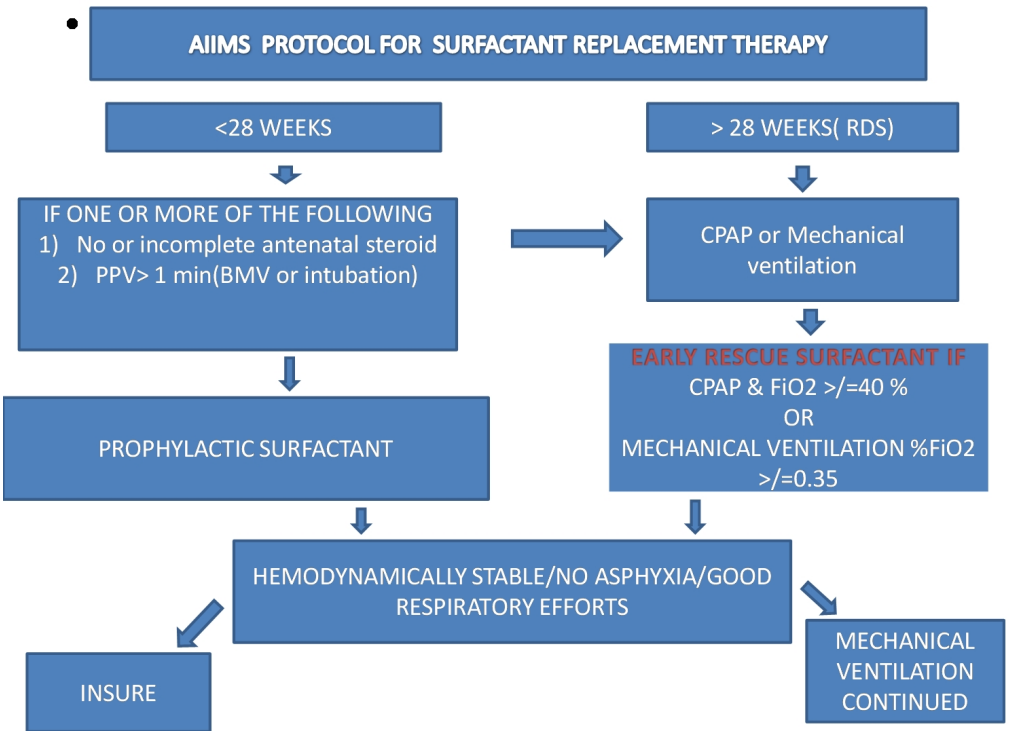
The disadvantages of prophylactic therapy

->there may occur a problem of instability in resuscitation.

-> may be an unnecessary treatment in some infants due to increased cost, increased risk of side effect.

may be no improvement neurologically.

-> un necessary intubation needed.



METHOD OF ADMINISTRATION OF SURFACTANT

1. A trained person should provide surfactant.

2. before using, warm it .

3. don't shake it.

4.intubate baby with appropriate sized tube.

5. check for equal distribution of airway.

6.vitals to be monitored.

7. Surfactant to be given through the feeding tube inserted in the ET tube.

8. Total dose given as bolus-four aliquots.

9. The neonate to be checked for wellbeing in between dose. So to be connected to a resuscitating machine.

10. After administering surfactant, ET suction should be avoided at least 2 hrs.

Administration.

To be done under aseptic precautions

Administration equipments needed

1 Syringe with specified dose of surfactant

2 Appropriate sized feeding tube or catheter, ETT connector with delivery port, or closed catheter system

3 Mechanical ventilator with tidal volume monitoring capability

Technique for instilling surfactant

One of the technique for prophylactic surfactant

InSurE

InSurE stands for Intubate – Surfactant – Extubate to CPAP.

InSurE comprises of intubation, surfactant administration, brief period of ventilation (usually < 1 hour) and rapid extubation to nasal CPAP.

Done mainly to prevent ventilation induced lung injury (VILI).

Benefits ->In neonates with signs and symptoms of RDS, InSurE to nasal CPAP results in decreased duration of mechanical ventilation, air leak and BPD.

Drawbacks -> severe birth asphyxia,

lack of complete course of antenatal steroids,

extreme prematurity,

reduces its efficacy

REPEATED DOSE OF SURFACTANT

Multiple doses had a stronger effect than single doses. Repeat doses of surfactant may be need when there is mucous plugging of the ET tube.

The risk of pulmonary hemorrhage following surfactant therapy is more common with natural surfactants (5% to 6%) than with synthetic surfactants (1% to 3%).

Also needed if the given surfactant is inhibited by edema fluid, soluble proteins and inflammatory mediators which are present in the alveoli after lung injury due to mechanical ventilation and in neonates with delayed surfactant administration or sepsis, lower gestation/birth weight and male sex.

Also when the neonate require FiO 0.4 or more on CPAP and 2 mechanical ventilation to maintain a target saturation.

Administering more than three doses wont show significant benefit.

POOR RESPONSE TO SURFACTANT

Some neonates may not show the expected response to the given surfactant (RDS plus).

These non responders either have

lung injury prior to birth (infection),

lung injury after birth and

prior to treatment (large tidal volume),

asphyxia, sepsis/pneumonia,

meconium aspiration,

severe disease,

pulmonary hypoplasia, or

concomitant cardiovascular (low blood pressure, congenital heart disease) conditions.

ADVERSE EFFECTS

Surfactant replacement therapy is a much safer one and usually there are transient side effects.

Hypoxia and bradycardia can occur during instillation because of acute airway obstruction.

Few less common acute adverse effects are reflux into the pharynx

increased PCO gagging and mucous plugging of ET tube.

Pulmonary hemorrhage typically occurs within 72 hrs ,due to the

improvement in lung compliance after therapy due to increase in left-to-right shunt through the PDA resulting in increased pulmonary blood flow and pulmonary congestion.

CONTRAINDICATIONS

Relative contraindications to surfactant administration are:

1. the presence of congenital anomalies

2. respiratory distress in infants with laboratory evidence

of lung maturity

3. diagnosis of congenital diaphragmatic hernia.

4. patient hemodynamically unstable

5. active pulmonary hemorrhage

REVIEW OF LITERATURE

1) Retinopathy of prematurity in a controlled trial of prophylactic surfactant treatment. Randomized controlled trial . Pennefather PM, et al. Br J Ophthalmol. 1996.

AIMS: To investigate the incidence of acute and cicatricial retinopathy of prematurity (ROP) in acohort of premature neonates entered into a randomised, multicentre trial of prophylactic

exogenous surfactant for respiratory distress syndrome (RDS) compared with controls receivingsurfactant only if severe RDS developed.

METHODS: The incidence of acute and cicatricial ROP was assessed in 304 neonates born atless than 30 weeks' gestation in a geographically defined population of approximately three

million.

RESULTS: There was a trend towards improved survival in the group receiving prophylactic

surfactant with 102/151 (67.5%) surviving compared with 82/141 controls (58.2%, p = 0.12). The prophylactic surfactant group would be expected to have an increased risk of ROP due to

improved survival, particularly of the most premature infants. However, there was no statistically significant difference in the incidence of acute ROP between the two groups and the incidence of cicatricial ROP was lower in the group receiving prophylactic surfactant (4/100 survivors,4.0%) compared with neonates receiving rescue surfactant as required (6/81, 7.4%). This difference did not reach statistical significance (p = 0.35).

2)Use and timing of surfactant administration: impact on neonatal outcomes in extremely low gestational age infants born in Canadian Neonatal Intensive Care Unit

Amelie Stritzke ORCID Icon, Khorshid Mohammad, Prakesh S. Shah, Xiang Y. Ye, Vineet Bhandari, Albert Akierman

Received 24 Apr 2017, Accepted 18 Jul 2017, Accepted author version posted online: 20 Jul 2017, Published online: 31 Jul 2017

Background: Use, timing and doses of surfactant in preterm infants are variable in practice in modern NICUs.

Objective: The objective of this study is to explore the association between use and timing of surfactant administration and common neonatal adverse outcomes in preterm infants withgestational age (GA) < 28 weeks.

Material and methods: Neonates admitted to a participating Canadian Neonatal Network NICUbetween 2013 and 2015 were studied. Infants were divided into three groups based on surfactant administration: none, early (within 30 min of life), and late surfactant (>30 min). Theprimary outcome was a composite of ≥2 predefined outcomes: bronchopulmonary dysplasia(BPD), retinopathy of prematurity (ROP) and severe neurological injury (intraventricularhemorrhage or intraventricular hemorrhage (IVH) grade III/IV ± periventricular leukomalacia).

Results: Of 2512 eligible neonates, 430 were in the early, and 1228 were in the late surfactantgroup. There was no difference in the primary outcome (p = .88). There was a slightly lowerrisk of late onset sepsis [25% versus 29%, adjusted odds ratio (aOR): 0.8; 95% CI: 0.6–0.9] andROP (12.4 versus 15%, aOR: 0.7; 95% CI: 0.5–0.9) in the early surfactant group.

Conclusions: In preterm neonates, early administration of surfactant within 30 min of life was not associated with an increased risk of the primary composite outcome, but did have decreased rates of late onset sepsis and ROP.

3) Retinopathy of prematurity in surfactant treated infants

S J A Rankin, T R J Tubman, H L Halliday, S S Johnston

Seventy six babies of less than 1500 g birthweight who had surfactant

replacement therapy for severe respiratory distress syndrome were studied to assess the presence and stage of subsequent retinopathy ofprematurity all infants who have received surfactant therapy for severe RDS in our unit have been recorded on a computer database. The first 19 babies were enrolled in the Collaborative European Multicentre study of surfactant replacement therapy for severe RDS.' This extensive database has included all infants receiving surfactant therapy since the conclusion of this trial.

They used Curosurf a natural surfactant derived from porcine lung which was given in a dose of 200 mg/kg of phospholipid. All babies had intermittent positive pressure ventilation (IPPV) and were receiving more than 40-60% 02'

A control group of 90 babies, matched for birth weight and gestational age, who did not have surfactant therapy were also studied.Threshold ROP or greater was found in 1*7% of the surfactant group and 7-8% of the controls.

For the babies of less than 1000 g birth weight 4-0% of the surfactant babies and 16.3% of the controls reached threshold disease or greater. It is concluded that surfactant therapy is not associated with an increased incidence or severity of severe ROP in this preterm population.

AIM AND OBJECTIVES

To compare prophylactic versus therapeutic surfactant administration in preterm babies and retinopathy of prematurity.

MATERIALS AND METHODS

STUDY DESIGN

Prospective Observational study

STUDY CENTRE:

• Department of Ophthalmology, Government Rajaji Hospital, Madurai.

•Neonatal intensive care unit, Institute of Paediatrics, Government Rajaji Hospital, Madurai.

STUDY PERIOD:

• This study was conducted for a period 10 months from January 2019 to September 2019.

SAMPLE SIZE:

• Total of 100 babies included in the study.

ETHICAL APPROVAL:

• Institutional ethical clearance was obtained from the ethical committee, Government Rajaji Hospital, Madurai.

INFORMED CONSENT:

• Informed Consent for the study is obtained in written statement from parents or guardian of all the babies before enrolment for the study.

SELECTION OF STUDY SUBJECTS:

100 babies fulfilling the eligibility criteria referred from Neonatology Intensive Care Unit, GRH, Madurai whom were given surfactant therapy

INCLUSION CRITERIA

1. Preterm infants < 34 weeks of gestation
2 Low birth weight babies < 1750gm
3. Babies who received surfactant therapy.

EXCLUSION CRITERIA

1. Preterm infants who have not received surfactant therapy
2. Neonates who did not survive the maximum ROP screening period
3. Babies of parent who are not consenting for the study

METHODOLOGY:

The various parameters recorded were weight at birth, gestational age , age of post conception, risk factors such as anaemia, long term exposure to oxygen, neonatal jaundice, mechanical ventilation, use of any surfactant , Respiratory Distress Syndrome, sepsis, multiple births, multiple blood transfusions and intraventricular haemorrhage.

Gestational age was calculated according to last menstrual period or

according to the date mentioned by first trimester USG abdomen.

In our study the screening protocol for ROP was followed based on the guidelines by National Neonatology Forum (NNF).

The first retinal examination would be held at 3 to 4 weeks from the birth.

Retina examined with binocular indirect ophthalmoscope with+20 D lens. Patient information and retinal findings recorded in the ROP screening case sheet. For categorising ROP, revised ICROP guidelines and classification was used. Followup schedule individualised based on the retinal findings and it would be continued till retina vascularises completely or ROP regression noted or until treated according to the ETROP guidelines.

In our study,

"Mild ROP"- was termed for ROP where the severity is not sufficient to meet the criteria for treatment according to "ETROP" and CRYO-ROP study and,

"Severe ROP"- was termed for either the Type 1 ROP based on "ETROP study" findings or the threshold ROP, Aggressive ROP, stage 4 ROP(partial RD)or stage 5 ROP(total RD) that validates treatment.

Babies in our study will be categorised into two groups as follows:

GROUP 1: Preterm low birth weight babies who received prophylactic surfactant therapy.

GROUP 2: Preterm low birth weight babies who received therapeutic surfactant therapy.

PROCEDURE:

- Procedure explained to babie's parents or the gaurdian.
- Informed written consent to be obtained.
- Oral feeds to be curtailed one hour before the procedure.
- Clean hands with disinfectant is the priority.
- Anterior segment of the eye would be examined before retinal examination to look for pupil size ,tunica vasculosalentis, , pupillary light reflex and lens status.
- Both the eyes are dilated with the mydriatics, as a combination of tropicamide 0.5% and phenylephrine 2.5% eye drops has to be prepared by diluting tropicamide 0.8% and phenylephrine 5% eye drop in tear substitutes in 50:50, and used two to three times about 10-15 minutes apart.
- Excess drops would be wiped off. This will prevent systemic absorption.
- Pupils are adequately dilated before the examination. If pupil is not fully dilated, gains significance as a sign for plus disease.
- Baby to be placed in examining couch in supine position.
- Anaesthetise the cornea with one drop of, 0.5% proparacaine is instilled in culdesac of both the eyes.

- Paediatric universal eye speculum is applied to the eye.
- Retina would be examined by Binocular Indirect Ophthalmoscope
- Using +20D lens and the retinal periphery is examined using sclera depressor.
- Posterior pole is to be examined for plus disease, and all clock hours are examined orderly and finally all clock hours of the retinal periphery.
- The retinal findings of ROP will be recorded with the help of fundus diagram using Amsler's color coding.

STATISTICAL ANALYSIS:

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer by using SPSS 16 software.

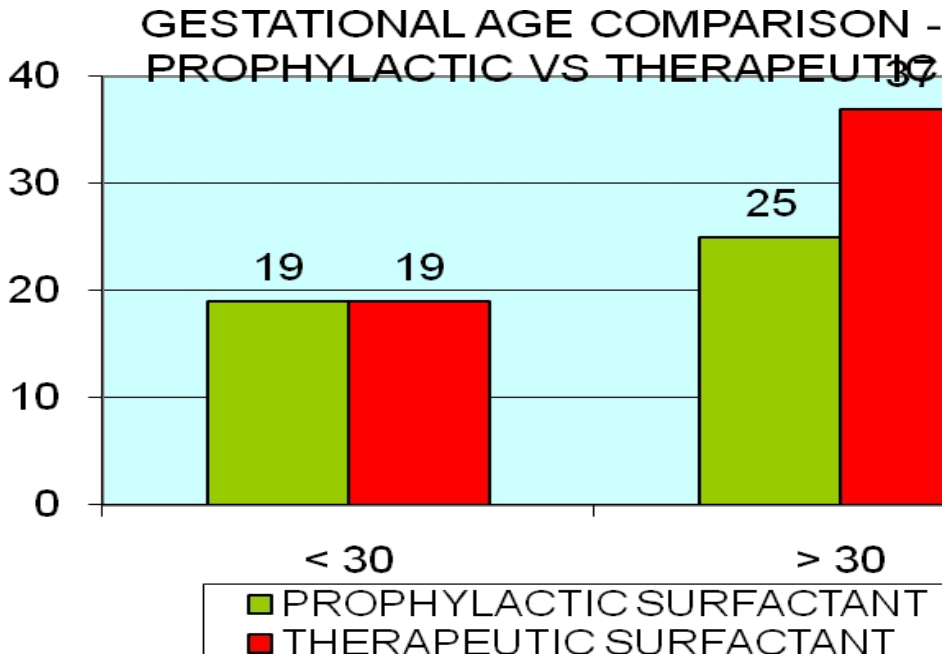
Using this software, percentages, means, standard deviations were calculated and 'p' values were calculated from Student 't' test for raw data and chi square test for consolidated data to test the significance of difference between variables.

A 'p' value less than 0.05 is taken to denote significant relationship.

OBSERVATIONAL ANALYSIS

TABLE 1:GESTATIONAL AGE

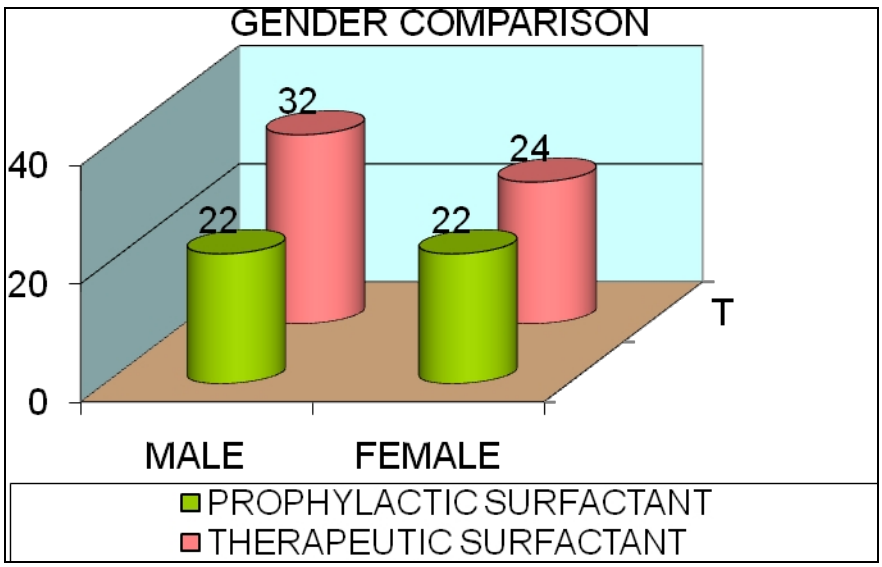
GESTATIONAL AGE (WEEKS)	PROPHYLACTIC SURFACTANT	THERAPEUTIC SURFACTANT
< 30	19	19
30 -34	25	37
TOTAL	44	56
Mean	30.818	31.179
SD	1.66	1.403
P' value	0.242 Not significant	



The mean gestational age in group 1 and group 2 were 3O.818 weeks and 31.178 weeks respectively and there is no significant difference in gestational age between 2 groups.(P = 0.242)

TABLE 2:GENDER

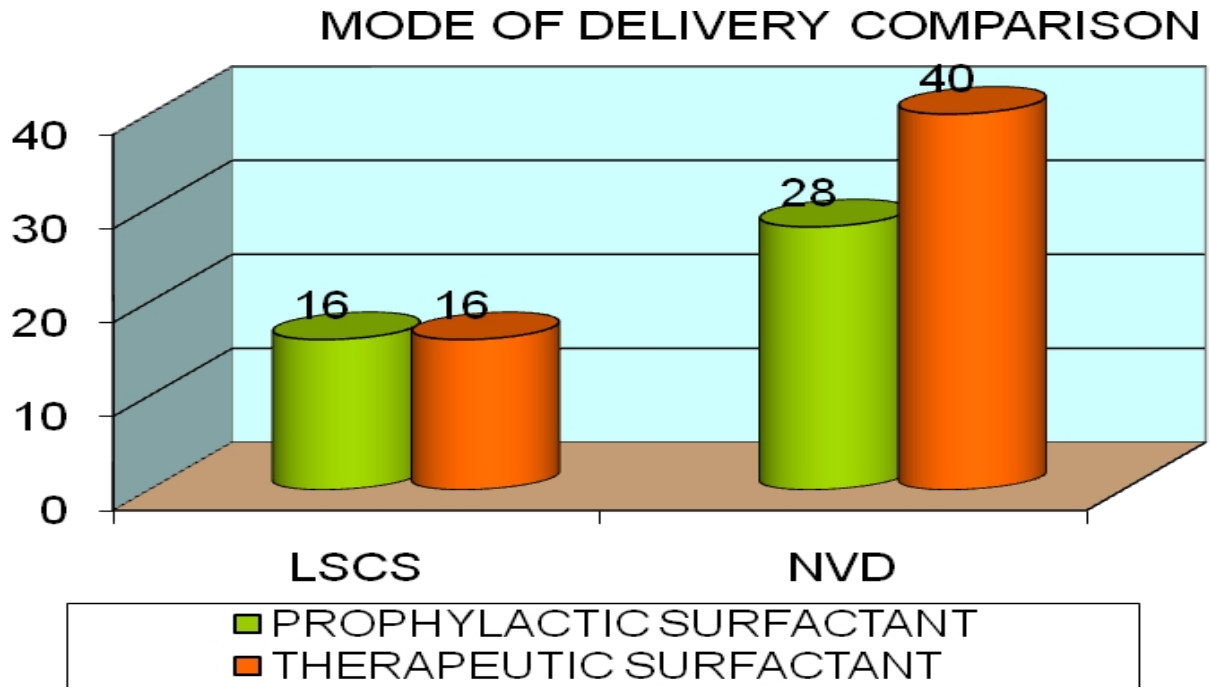
Gender	PROPHYLACTIC SURFACTANT	THERAPEUTIC SURFACTANT	Total
MALE	22	32	54
FEMALE	22	24	46
TOTAL	44	56	100
P' value	0.611 Not significant		



Among 100 babies analysed, 44 were males and 56 were females. Group 1 had 22 males and 22 females also Group 2 had 32 males and 24 females. There was no significant association of gender within both the groups, since the 'p' value was 0.611.

TABLE 3: MODE OF DELIVERY

MODE OF DELIVERY	PROPHYLACTIC SURFACTANT	THERAPEUTIC SURFACTANT	TOTAL
LSCS	16	16	32
NVD	28	40	68
TOTAL	44	56	100
P' value	0.54 Not significant		

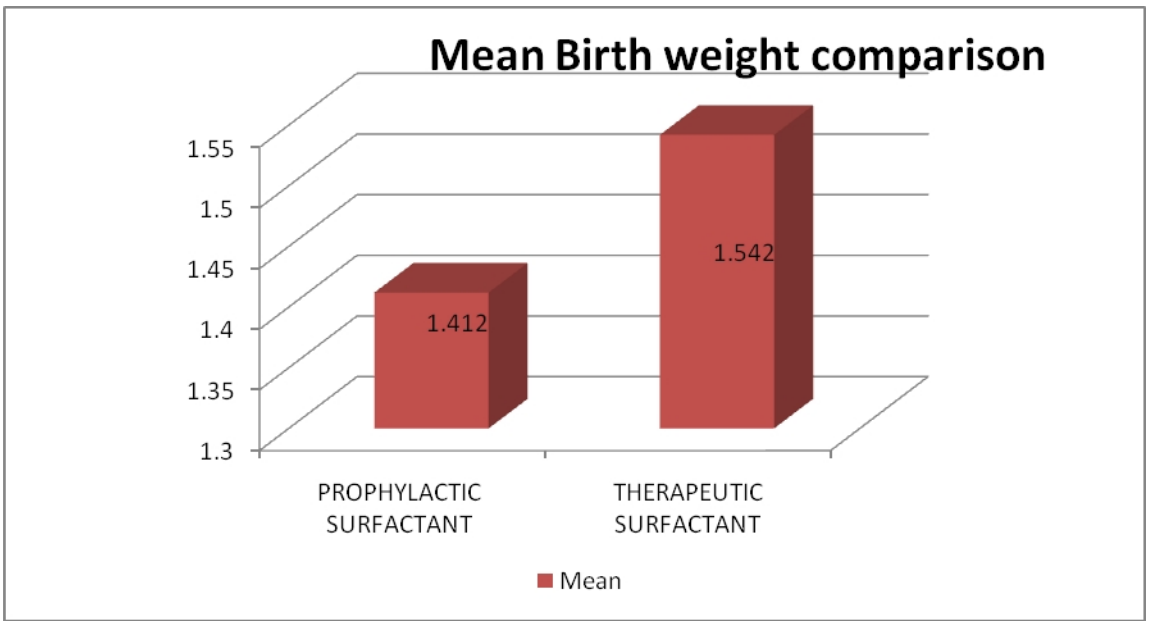


Among 100 babies, 68 were normal vaginal delivery and 32 were LSCS.

Group 1 had 28 NVD cases and 16 LSCS cases and group 2 had 40 NVD cases and 16 LSCS cases. There was no significant association between two types of mode of delivery in both the groups. (P = 0.54)

TABLE 4: BIRTH WEIGHT

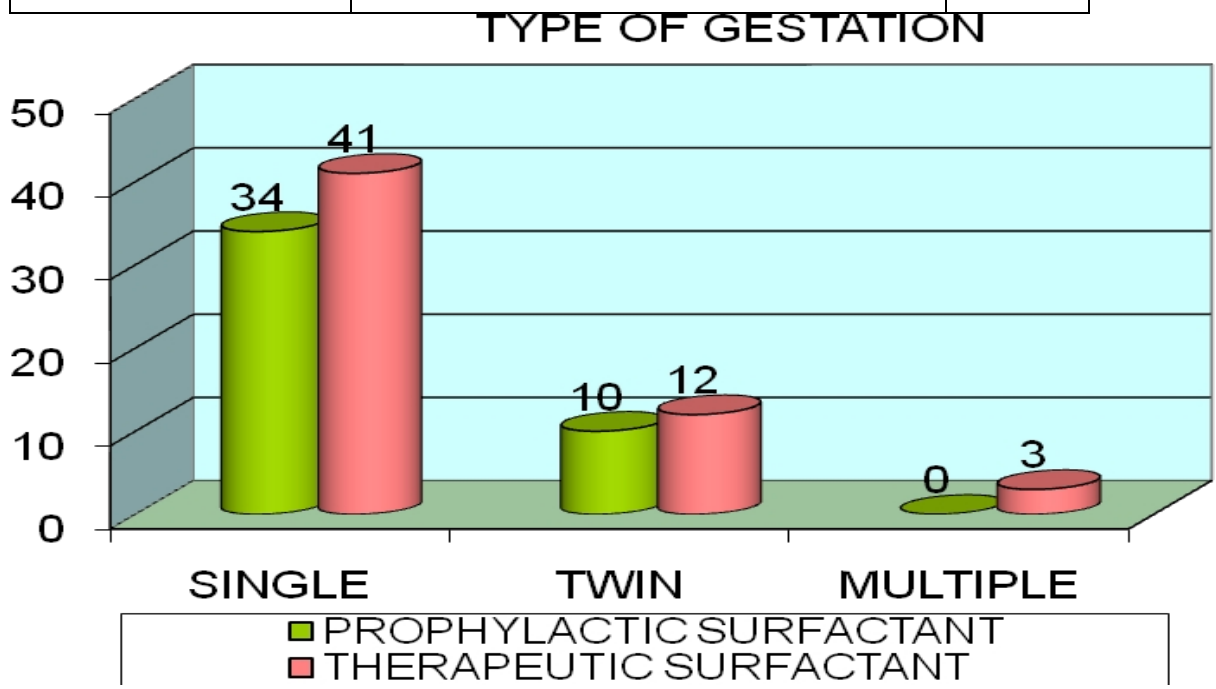
BIRTH WEIGHT (KG)	PROPHYLACTIC SURFACTANT	THERAPEUTIC SURFACTANT
< 1.25	16	7
> 1.25	28	49
TOTAL	44	56
Mean	1.412	1.542
SD	0.283	0.222
P' value	0.011 Significant	



The mean birth weight in group 1 and group 2 were 1.412grams and 1.542 grams respectively and no significant difference was found between the two groups.(P = 0.11)

TABLE 5:TYPE OF GESTATION

TYPE OF GESTATION	PROPHYLACTIC SURFACTANT	THERAPEUTIC SURFACTANT	TOTAL
SINGLE	34	41	75
TWIN	10	12	22
MULTIPLE	0	3	3
TOTAL	44	56	100
P' value	0.297 Not significant		



Among 100 babies, 75 were single gestation and 22 were twin gestation, 3 were multiple gestation Group1had 34 single gestation babies and 10 twin gestation babies and group2 had 3841single gestation and 12 twin gestation babies and 3 multiple gestation babies. There was no significant difference in type of gestation between two groups.(P = 0.297)

TABLE 6: FETAL RISK FACTORS

FETAL RISK FACTORS	PROPHYLACTIC	THERAPEUTIC

	SURFACTANT	SURFACTANT
BIRTH ASPYXIA	0	1
CPAP	1	0
HIE	1	1
IUGR	1	0
MSAF	3	1
NNJ	4	3
MV	0	6
OUTBORN	0	1
PERINATALASPHYXIA	0	1
PERINATALDEPRESSION	0	4
RDS	O	35
SEPSIS	0	4
NO specific risk factors	32	0
TOTAL	42	60
P' value	<0.001 Significant	

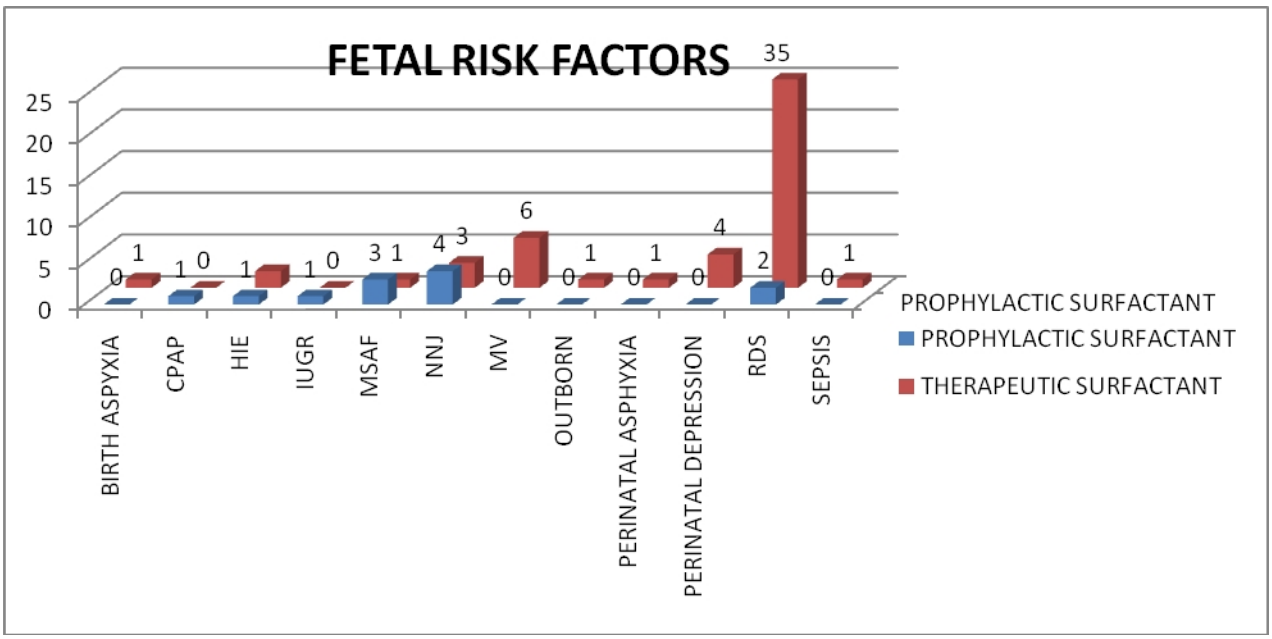
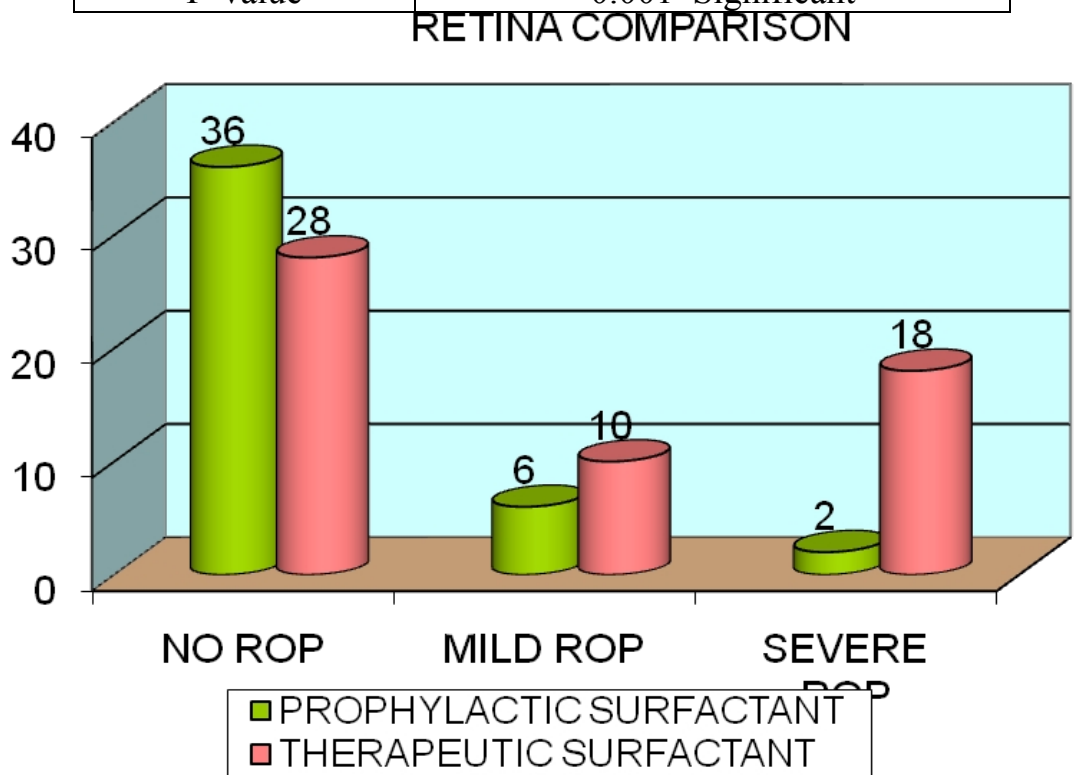


TABLE 7:SEVERITY OF ROP

RETINA	PROPHYLACTIC SURFACTANT	THERAPEUTIC SURFACTANT

NO ROP	36	28
MILD ROP	6	10
SEVERE ROP	2	18
TOTAL	44	56
P' value	<0.001 Significant	



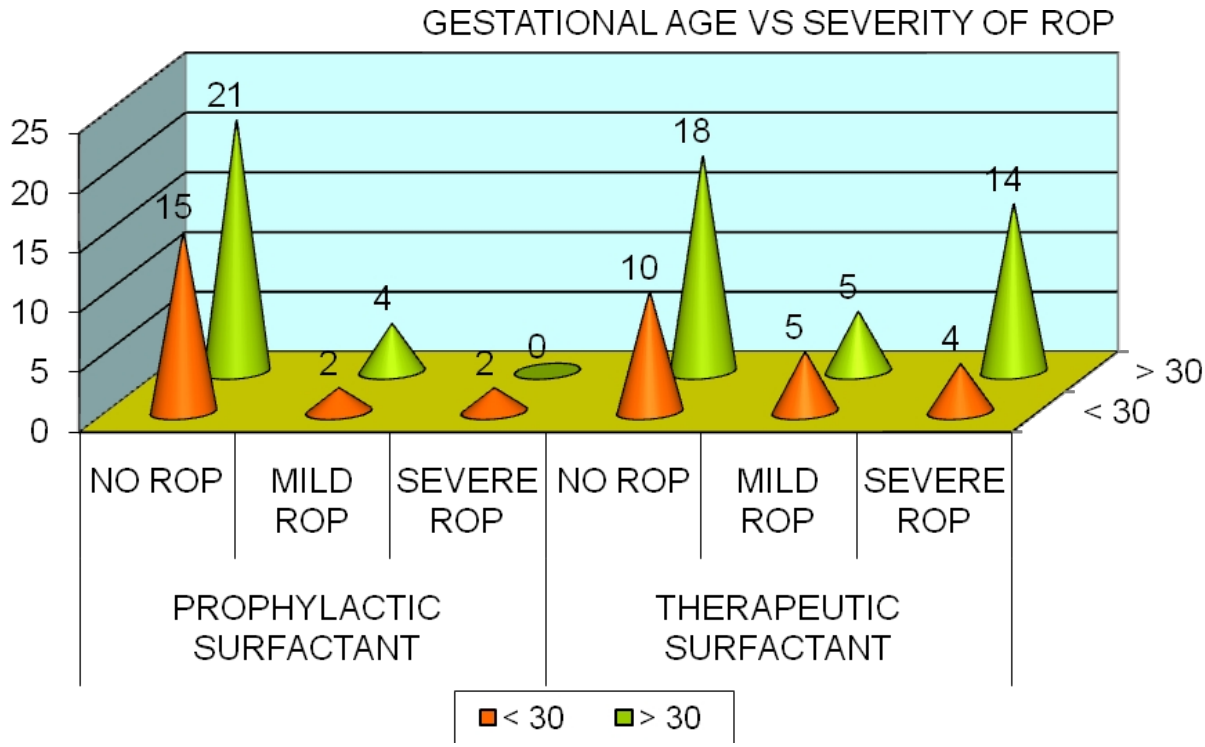
Among 100 babies, 20 were severe ROP cases, 16 mild ROP cases and 54 were No ROP cases. Group 1 had 2 severe ROP cases, 6 mild ROP cases, 36 No ROP cases .Group 2 had 18 severe ROP cases,10 mild ROP cases and 36 No ROP cases. The incidence of severe ROP was found to be more among surfactant given babies.

Statistical analysis showed, there is significant association between retinal findings in both the groups. (P <0.001).

TABLE – 8 GESTATIONAL AGE VS SEVERITY OF ROP

GESTATIONAL AGE (WEEKS)	PROPHYLACTIC SURFACTANT	THERAPEUTIC SURFACTANT

	NO ROP	MILD ROP	SEVERE ROP	NO ROP	MILD ROP	SEVERE ROP
< 30	15	2	2	10	5	4
30 - 34	21	4	0	18	5	14
Total	36	6	2	28	10	18

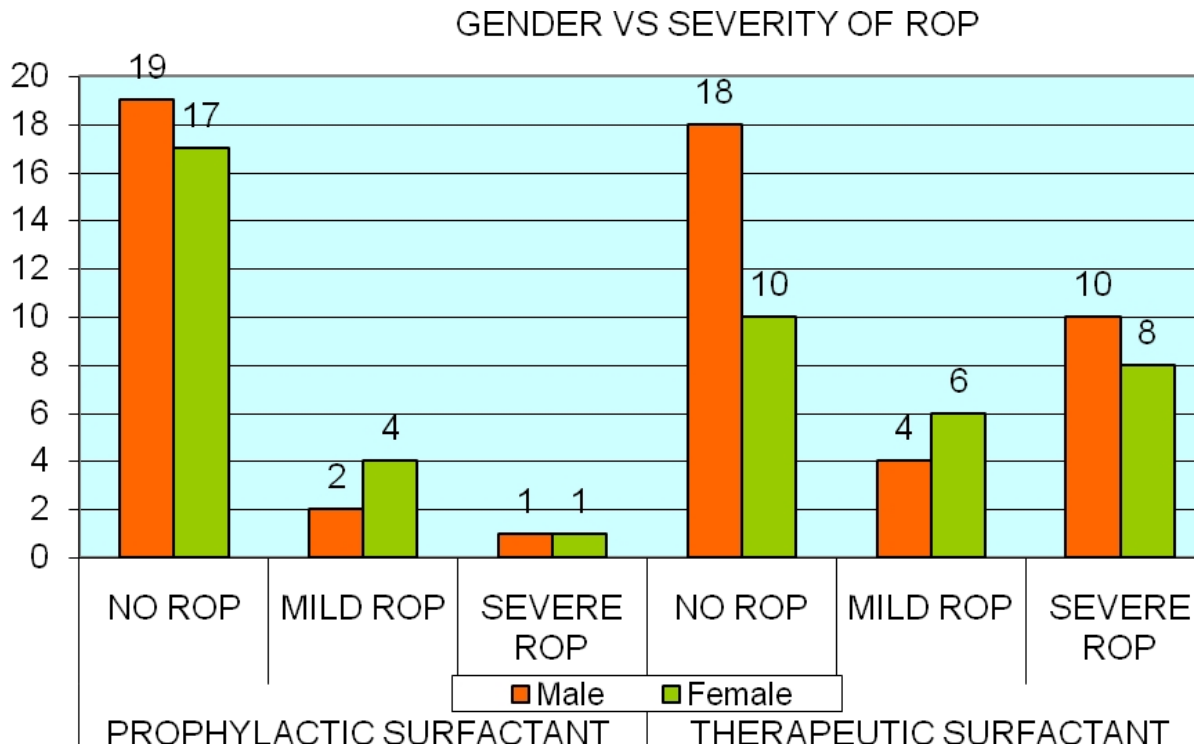


In Group 1, occurrence of Severe ROP on comparing gestational age <30 weeks and > 30 weeks shows p value 0.234. In Group 2 ,occurrence of sever ROP in group 2 shows p value 0.318.both are not statistically significant.

TABLE 9:GENDER AND SEVERITY OF ROP

Gender	PROPHYLACTIC SURFACTANT	THERAPEUTIC SURFACTANT

	NO ROP	MILD ROP	SEVERE ROP	NO ROP	MILD ROP	SEVERE ROP
Male	19	2	1	18	4	10
Female	17	4	1	10	6	8
Total	36	6	2	28	10	18

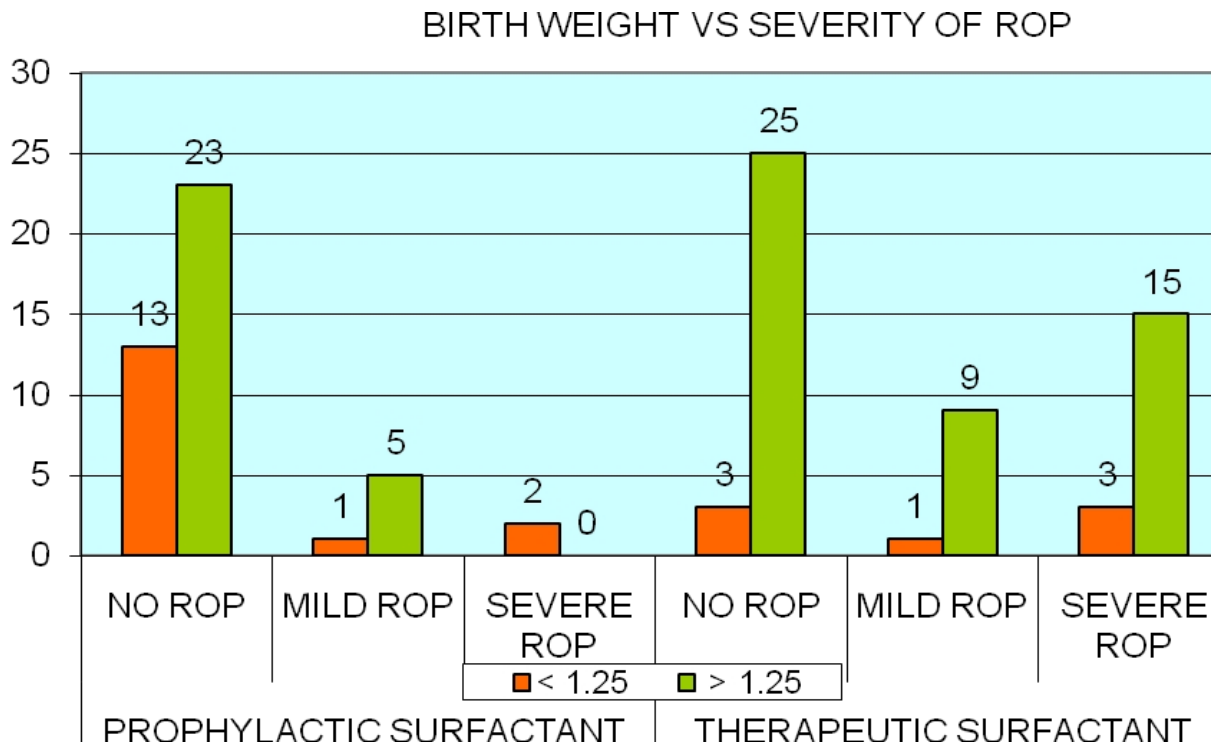


In Group 1, among male and female occurrence of severity of ROP shows P value as 0.678 and in Group 2 its 0.406. Both are not statistically significant.

TABLE 10 : BIRTH WEIGHT AND SEVERITY OF ROP

Birth weight	PROPHYLACTIC SURFACTANT			THERAPEUTIC SURFACTANT		
	NO ROP	MILD ROP	SEVERE ROP	NO ROP	MILD ROP	SEVERE ROP

< 1.25	13	1	2	3	1	3
> 1.25	23	5	0	25	9	15
Total	36	6	2	28	10	18

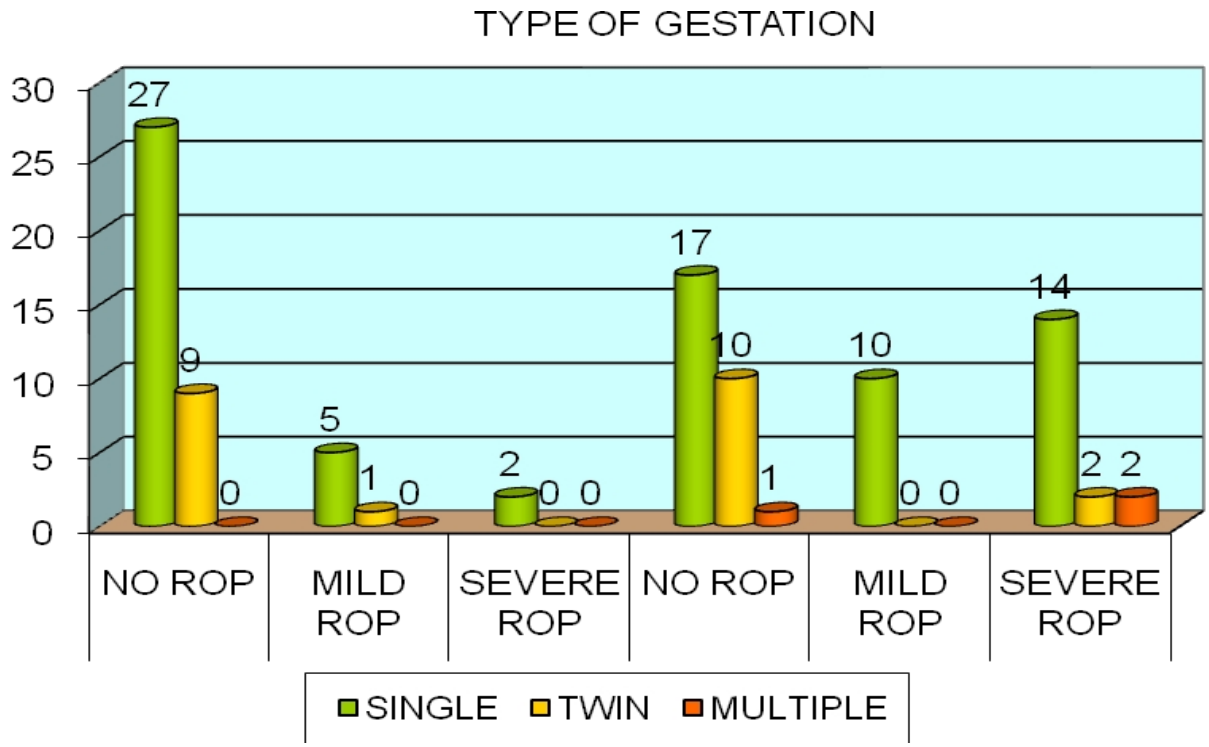


In Group 1, occurrence of Severe ROP on comparing birth weight <1.25 and > 1.25 shows p value 0.105. In Group 2 ,occurrence of sever ROP in group 2 shows p value 0.809.Both are not statistically significant.

Table 11: TYPE OF GESTATION

TYPE OF GESTATION	PROPHYLACTIC SURFACTANT			THERAPEUTIC SURFACTANT		
	NO ROP	MILD ROP	SEVERE ROP	NO ROP	MILD ROP	SEVERE ROP
SINGLE	27	5	2	17	10	14
TWIN	9	1	0	10	0	2

MULTIPLE	0	0	0	1	0	2
TOTAL	36	6	2	28	10	18



In Group 1, among single, twin and multiple gestational ages and occurrence of severe ROP ,p value shows 0.105 and in group 2 shows 0.809.both are not statistically significant.

SUMMARY OF RESULTS

- Among 100 babies taken for the study , 20 had severe ROP ; 16 had mild ROP and 54 had No ROP .
- Among 100 babies analysed, 54 were males and 46 were females. Group

1 had 22 males and 22 females also Group 2 had 32 males and 24 females. There was no significant association of gender between the groups, since the 'p' value was 0.611.

- The mean gestational age in group 1 and group 2 were 30.818 weeks and 31.719 weeks respectively and there is no significant difference in gestational age between the two groups.(P = 0.242)
- The mean birth weight in group 1 and group 2 were 1.412 grams and 1.542 grams respectively and significant difference was found between the two groups.(P = 0.011).
- Among 100 babies, 58 were normal vaginal delivery and 32 were LSCS. Group 1 had 28 NVD cases and 16 LSCS cases and group 2 had 40 NVD cases and 16 LSCS cases. There was no significant association between two types of mode of delivery in both the groups. (P = 0.54)

*In this study, prophylactic surfactant is given to 44 babies and therapeutic surfactant to 56 babies

* In Group 1, among male and female occurrence of severity of ROP shows P value as 0.678 and in Group 2 its 0.406.both are not statistically significant.

* In Group 1, occurrence of Severe ROP on comparing gestational age <30 weeks and 30 - 34 weeks shows p value 0.234. In Group 2 ,occurrence of

severe ROP in group 2 shows p value 0.318.both are not statistically significant.

- In Group 1, occurrence of Severe ROP on comparing birth weight <1.25 and > 1.25 shows p value 0.105. In Group 2 ,occurrence of sever ROP in group 2 shows p value 0.809.Both are not statistically significant.
- Among 100 babies , 20 were severe ROP cases, 16 mild ROP cases and 54 were No ROP cases. Group 1 had 2 severe ROP cases, 6 mild ROP cases, 36 No ROP cases .Group 2 had 18 severe ROP cases,10 mild ROP cases and 36 No ROP cases. The incidence of severe ROP was found to be more among surfactant given babies.

Statistical analysis showed, there is significant association between retinal findings in both the groups. (P <0.001).

This study shows significant association between therapeutic surfactant administration and severe ROP than prophylactic surfactant administration. Also shows the need for mechanical ventilation is more in therapeutic surfactant babies which can increase the risk of ROP.

DISCUSSION

- Retinopathy Of Prematurity (ROP) ,is an abnormal retinal vascular development during postnatal period .postnatal risk fctors which have a predictive value in development and severity of ROP in screening, diagnosing and treating the ROP at an appropriate time.

- Main aim is acquiring good visual benefit and reduction in ROP sequlae if which can be achieved by a timely intervention of ROP.
- ROP being one of the leading cause of blindness among children, is a disease of the developing in retinal vasculature . The pathogenesis here is the disturbance of relative hypoxic state which is essential for normal vascular growth. In ROP there is an imbalance between hypoxia-hyperoxia state leading to the growth of abnormal vessels.
- Hypoxia, followed by hyperoxic state leads to a proliferative phase, which results as a consequence of alterations in the level of local vascular endothelial growth factor (VEGF) and the systemic insulin-like growth factor 1 (IGF-1). In normal state, VEGF is a vasoproliferative factor needed for the growth of retinal vessels and endothelial cell survival.
- However, VEGF can promote vessel growth only in combination with sufficient serum levels of IGF-1 which is deficient in premature infants

due to lack of maternal sources. Therefore, VEGF starts to accumulate as the metabolic demand of the retina increases. As the age and size of the baby increases, endogenous production of IGF-1also rises, thus promoting the VEGF activity and ultimately proliferative retinopathy develops as a result of highly accumulated VEGF.

*There are multiple risk factors implicated in genesis of ROP. It suggests a common thread is neonatal illness with disturbed homeostasis upsetting the delicately balanced retinal development process.

*ROP progression is determined by the severity of early insult to immature retina and is less influenced by prolonged or added adverse effects.

*Surfactant administration to preterm babies results in increase in pao2 with marked hyperoxia within a short time resulting in a period of instability with hyperoxia.

*Use of surfactant as a prophylactic therapy is on increase in recent years in the neonates at risk o developing RDS.

*S J A Rankin et al signifies that Surfactant administered in the early hours of babies birth has been shown to have significant advance in improving the survival rate of the preterm babies.

*Seiberth et al reported surfactant administration as a risk factor for ROP. Surfactant use has resulted in reduced infant mortality and morbidity primarily through improved lung function.

*Multicentre OSIRS trial tells prophylactic surfactant reduces the mean time on oxygen dependence like mechanical ventilation and there is reduced severe ROP incidence. but the difference is not statistically significant.

*Our study shows decrease in need of mechanical ventilation in prophylactic group hence avoiding fluctuating oxygen levels and ROP.

*Kalina enlightened that increased survival of low birth weight infants and their prolonged oxygen dependence may increase risk of ROP. Accordingly decreasing severity of early insult will decrease risk of severe ROP.

* Newer pharmacological treatments to improve the physiologic retinal vascularisation were "erythropoietin supplementation, IGF-1 supplementation, omega 3 polyunsaturated fatty acid supplementation" have shown good results in animal studies, but more work is needed before considered for use in preterm infants.

*Many randomized clinical trials found out the essential nutrient – "inositol" which reduces the severity of ROP. Currently, a multicentre randomized clinical trial is underway.

CONCLUSION

- Our study showed that babies who had prophylactic Surfactant administration compared to therapeutic surfactant administration showed reduced incidence in severity of ROP.
- When Surfactant administration is present in preterm low birth weight

babies and if its therapeutic also it should be considered as an independent risk factor for ROP. Followup and screening to be increased in babies who had therapeutic surfactant administration in postnatal period.

- ❖ When surfactant administered babies are screened for ROP regularly, it will help to detect the ROP timely and treatment can be delivered at its earliest. Thus reducing the devastating sequeale of ROP. It is also helpful to avoid unnecessary stressful examination on preterm infants who are not at risk of developing "severe ROP".
- ❖ Our study result helps the ophthalmologists and the neonatologists to look into the surfactant administered babies with special care and attention ,and to predict and closely followup for retinopathy changes much earlier before it is being diagnosed by the regular ophthalmic examination. It will help to intervene early and to prevent sight threatening complications.

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PROFOMA

NAME OF THE BABY	
GENDER	
POST NATAL AGE	
DATE OF SCREENING	
OP/ IP NUMBER	
NAME OF THE PARENT	
ADDRESS	

SINGLE OR MULTIPLE BIRTHS	
DOB	
BIRTH PLACE	
BIRTH WEIGHT	
LMP	
EDD	
GESTATION AGE AT BIRTH	
POST CONCEPTIONAL AGE	
MODE OF DELIVERY	
MATERNAL FACTORS	**Anaemia/PIH/Diabetes/Preeclampsia/Ecclampsia**
FETAL RISK FACTORS	**RDS/Apnea/Mechanical ventilation/CPAP/oxygen supplement**
SURFACTANT THERAPY	**PROPHYLACTIC**
	THERAPEUTIC
SYSTEMIC EXAMINATION	**CVS**
	RS
	CNS

OCULAR EXAMINATION

ANTERIOR SEGMENT

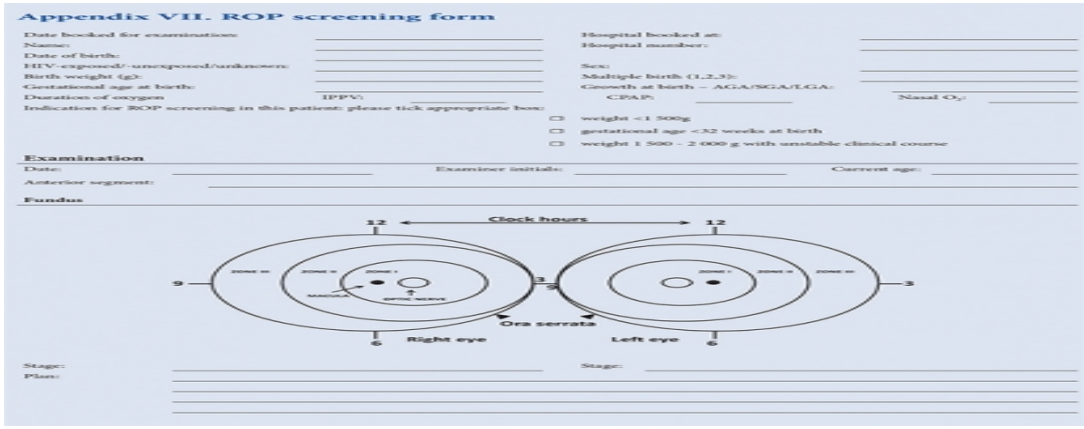
OD		**OS**
	LIDS	
	CONJUNCTIVA	

	CORNEA **TRANSPARENCY**	
	ANTERIOR CHAMBER	
	IRIS	
	PUPIL **SIZE** **COLOUR**	
	LENS	
POSTERIOR SEGMENT		
OD		**OS**
	MEDIA	
	DISC	
	RETINAL VESSELS	

	ROP – ZONE/ STAGE	
	CLOCK HOURS INVOLVED	
	FOVEA	
	PLUS DISEASE	

Fundus diagram:

VISIT: 1



Appendix VII. ROP screening form

Date booked for examination:
Name:
Date of birth:
HIV-exposed/-unexposed/unknown:
Birth weight (g):
Gestational age at birth:
Duration of oxygen IPPV:
Indication for ROP screening in this patient: please tick appropriate box:

Hospital booked at:
Hospital number:
Sex:
Multiple birth (1,2,3):
Growth at birth – AGA/SGA/LGA:
CPAP: Nasal O_2:

☐ weight <1 500g
☐ gestational age <32 weeks at birth
☐ weight 1 500 - 2 000 g with unstable clinical course

Examination
Date: Examiner initials: Current age:
Anterior segment:
Fundus

Stage:
Plan:
Stage:

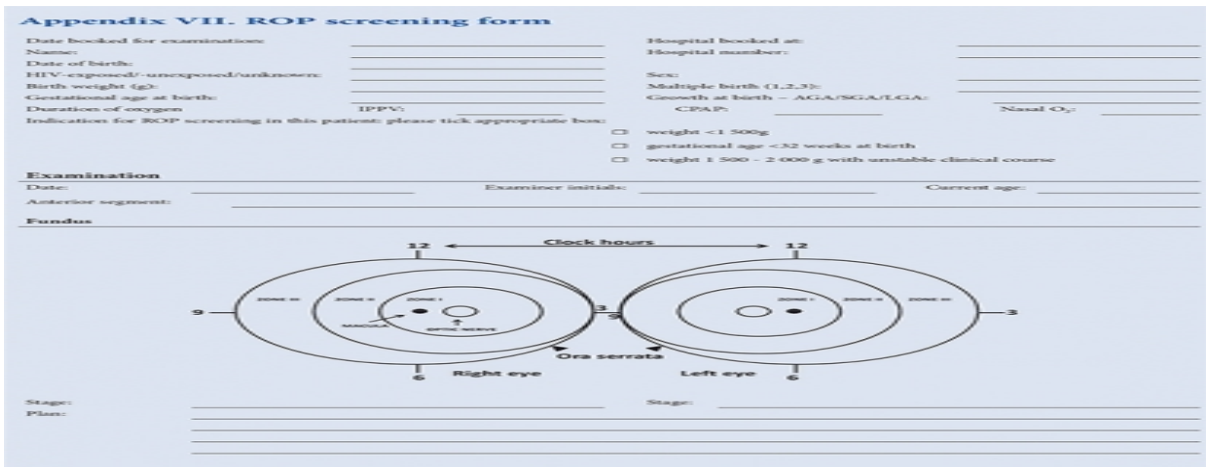
DIAGNOSIS

TREATMENT PLAN

FOLLOWUP ADVICE

FOLLOW UP DETAILS: No of visits/Date

VISIT: 2



Appendix VII. ROP screening form

Date booked for examination:
Name:
Date of birth:
HIV-exposed/-unexposed/unknown:
Birth weight (g):
Gestational age at birth:
Duration of oxygen IPPV:
Indication for ROP screening in this patient: please tick appropriate box:

Hospital booked at:
Hospital number:
Sex:
Multiple birth (1,2,3):
Growth at birth – AGA/SGA/LGA:
CPAP: Nasal O_2:

☐ weight <1 500g
☐ gestational age <32 weeks at birth
☐ weight 1 500 - 2 000 g with unstable clinical course

Examination
Date: Examiner initials: Current age:
Anterior segment:
Fundus

Stage:
Plan:
Stage:

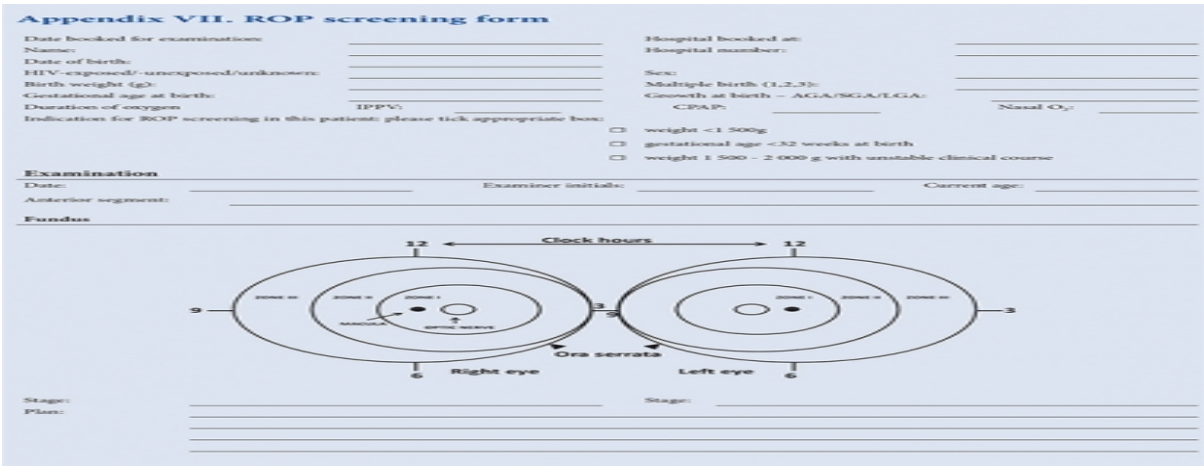
DIAGNOSIS FOLLOWUP

ADVICE

TREATMENT PLAN FOLLOW UP

DETAILS: No of visits/Date

VISIT: 3


Appendix VII. ROP screening form

Date booked for examination:
Name:
Date of birth:
HIV-exposed/ unexposed/unknown:
Birth weight (g):
Gestational age at birth:
Duration of oxygen IPPV:
Indication for ROP screening in this patient: please tick appropriate box:

Hospital booked at:
Hospital number:
Sex:
Multiple birth (1,2,3):
Growth at birth – AGA/SGA/LGA:
CPAP: Nasal O_2:

- weight <1 500g
- gestational age <32 weeks at birth
- weight 1 500 - 2 000 g with unstable clinical course

Examination
Date: Examiner initials: Current age:
Anterior segment:
Fundus

Stage:
Plan:
Stage:

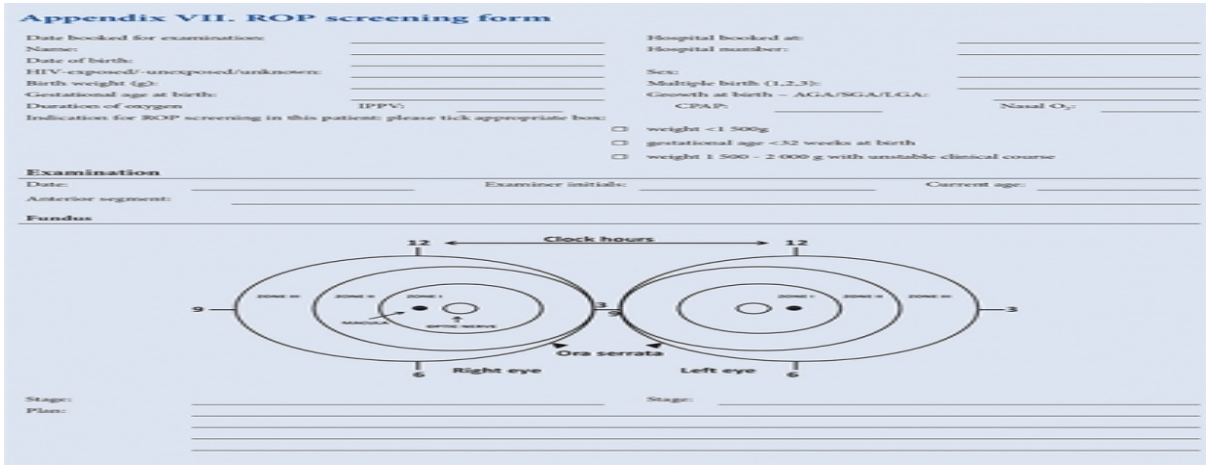
DIAGNOSIS

TREATMENT PLAN

FOLLOWUP ADVICE

FOLLOW UP DETAILS: No of visits/Date

VISIT: 4



Appendix VII. ROP screening form

Date booked for examination:
Name:
Date of birth:
HIV-exposed/ unexposed/unknown:
Birth weight (g):
Gestational age at birth:
Duration of oxygen IPPV:
Indication for ROP screening in this patient: please tick appropriate box:

Hospital booked at:
Hospital number:
Sex:
Multiple birth (1,2,3):
Growth at birth – AGA/SGA/LGA:
CPAP: Nasal O_2:

- ☐ weight <1 500g
- ☐ gestational age <32 weeks at birth
- ☐ weight 1 500 – 2 000 g with unstable clinical course

Examination

Date: Examiner initials: Current age:
Anterior segment:

Fundus

Stage:
Plan:
Stage:

DIAGNOSIS

TREATMENT PLAN

FOLLOW UP DETAILS: No of visits/Date

KEYS TO MASTER CHART

GA GESTATIONAL AGE

BW BIRTH WEIGHT

RDS RESPIRATORY DISTRESS SYNDROME

O_2 OXYGEN

MV MECHANICAL VENTILATION

LSCS LOWER SEGMENT CAESERIAN SECTION

NVD NORMAL VAGINAL DELIVERY

HIE HYPOXIC ISCHAEMIC ENCEPHALOPATHY

PIH PREGNANCY INDUCED HYPERTENSION

NNJ NEONATAL JAUNDICE

MSAF MECONIUM STAINED AMNIOTIC FLIUD

PPROM PREMATURE RUPTURE OF MEMRANE

NEC NECROTISING ENTEROCOLITIS

CHD CONGENITAL HEART DISEASE

ABBREVIATION

ROP RETINOPATHY OF PREMATURITY

GA GESTATIONAL AGE

BW BIRTH WEIGHT

ET-ROP THE EARLY TREATMENT FOR RETINOPATHY OF PREMATURITY

RLF RETROLENTAL FIBROPLASIA

CRYO-ROP	CRYOTHERAPY FOR RETINOPATHY OF PREMATURITY
LIGHT-ROP	THE EFFECT OF LIGHT REDUCTION ON RETINOPATHY OF PREMATURITY
VEGF	VASCULAR ENDOTHELIAL GROWTH FACTOR
IGF-1	INSULIN LIKE GROWTH FACTOR 1
CA	CHRONOLOGICAL AGE
PMA	POST MENSTRUAL AGE
NNF	NATIONAL NEONATOLOGY FORUM
ICROP	THE INTERNATIONAL CLASSIFICATION FOR RETINOPATHY OF PREMATURITY
AP-ROP	AGGRESSIVE POSTERIOR POLE RETINOPATHY OF PREMATURITY
PHPV	PERSISTANT HYPERPLASTIC PRIMARY VITREOUS
BEAT-ROP	BEVACIZUMAB ELIMINATES THE ANGIOGENIC THREAT OF RETINOPATHY OF PREMATURITY

MADURAI MEDICAL COLLEGE
MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.A.Ragul
Designation	:	PG in MD., Anaesthesia
Course of Study	:	2017- 2020
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	Comparison of Bupivacaine and Ropivacaine in Labour Analgesia
Ethical Committee as on	:	02.07.2019

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College
Madurai

DEAN
Madurai Medical College
Madurai-20

09 AUG 2019

URKUND

Urkund Analysis Result

Analysed Document:	RETINOPATHY OF PREMATURITY FOR THESIS.docx (D57463001)
Submitted:	10/22/2019 3:50:00 PM
Submitted By:	ramuso3o7@gmail.com
Significance:	5 %

Sources included in the report:

https://clinicalgate.com/retinopathy-of-prematurity/
https://www.ncbi.nlm.nih.gov/pubmed/1390486
https://www.researchgate.net/publication/21764199_Retinopathy_of_prematurity_in_surfactant_treated_infants
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2399513
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2886250/
9239ce92-89c6-4a2a-925a-54f77d11d25b
https://entokey.com/macular-disease-secondary-to-peripheral-retinal-vasculopathy-2/

Instances where selected sources appear:

15

S.NO	NAME	GESTATIONAL AGE (WEEKS)	BIRTH WEIGHT (KG)	SEX	MODE OF DELIVERY	TYPE OF GESTSTION	MATERNAL RISK FACTORS	FETAL RISK FACTORS	PROPHYLACTIC SURFACTANT	THERAPEUTIC SURFACTANT	RETINA - NO ROP	RETINA - MILD ROP	RETI SEVI RO
1	B/0 SELVI	30	1.69	M	NVD	SINGLE	-		PROPHYLACTIC		NO ROP		
2	B/O SARANYA	31	1.82	F	NVD	SINGLE	ANEMIA		PROPHYLACTIC		NO ROP		
3	B/O VIJAYA	31	1.2	F	LSCS	SINGLE		RDS/MV		THERAPEUTIC		MILD ROP	
4	B/O KALEESWARI	30	1.15	M	LSCS	SINGLE	PIH		PROPHYLACTIC		NO ROP		
5	B/O ESWARI	31	1.6	M	NVD	SINGLE	SEPSIS	RDS		THERAPEUTIC	NO ROP		
6	B/O MUNISWARI	30	1.56	M	NVD	SINGLE			PROPHYLACTIC		NO ROP		
7	B/O MUTHUMARI	29	1.20	F	NVD	SINGLE	HYPOTHYROID		PROPHYLACTIC		NO ROP		
8	B/O LATHA	32	1.00	M	NVD	SINGLE			PROPHYLACTIC		NO ROP		
9	B/O PRIYANKA	30	1.7	F	NVD	SINGLE		MV		THERAPEUTIC		MILD ROP	
10	B/O MEENATCHI	30	1.9	F	NVD	SINGLE		BIRTH ASPYXIA		THERAPEUTIC		MILD ROP	
11	B/O ANGAMMAL	31	1.4	M	NVD	SINGLE		OUTBORN/MV		THERAPEUTIC		MILD ROP	
12	B/O PANDEESWARI	31	1.7	M	NVD	MULTIPLE		MSAF		THERAPEUTIC			SEVI RO
13	B/O ANANDHI	31	1.1	M	NVD	MULTIPLE		HIE		THERAPEUTIC			SEVI RO
14	B/O VALLIESWARI	29	1.50	F	NVD	SINGLE		HIE	PROPHYLACTIC		NO ROP		
15	B/O JAYA	32	1.7	F	NVD	SINGLE		MV		THERAPEUTIC			SEVI RO
16	B/O NAGALAKSHMI	28	1.70	M	LSCS	SINGLE	PIH		PROPHYLACTIC			MILD ROP	
17	B/O MAJU	32	1.5	F	NVD	SINGLE	GDM	BIRTH ASPYXIA		THERAPEUTIC			SEVI RO

18	B/O SIVARANI	31	1.75	M	LSCS	SINGLE	PROM	CPAP	PROPHYLACTIC			MILD ROP	
19	B/O KARPAGAM	31	1.6	M	LSCS	MULTIPLE		MV		THERAPEUTIC	NO ROP		
20	B/O RAKKU	31	1.75	F	LSCS	SINGLE		MV		THERAPEUTIC			SEVI RO
21	B/OVIJAYALAKSMI	31	1.9	M	NVD	SINGLE		RDS		THERAPEUTIC			SEVI RO
22	B/O PANDISELVI	32	1.90	M	NVD	SINGLE		MSAF	PROPHYLACTIC		NO ROP		
23	B/O MAHALAXMI	30	1.42	M	NVD	SINGLE			PROPHYLACTIC		NO ROP		
24	B/O REVATHY	31	1.6	M	NVD	SINGLE		RDS		THERAPEUTIC	NO ROP		
25	B/O MURUGESWARI	32	1.71	F	NVD	SINGLE		RDS		THERAPEUTIC	NO ROP		
26	B/O MUTHUMEENA	32	1.74	F	LSCS	SINGLE	PROM		PROPHYLACTIC		NO ROP		
27	B/O PREMA	31	1.6	M	NVD	SINGLE		SEPSIS/RDS		THERAPEUTIC	NO ROP		
28	B/O VINITHA	32	1.20	F	NVD	SINGLE	HYPOTHYROID		PROPHYLACTIC		NO ROP		
29	B/O VENI	30	1.75	F	LSCS	SINGLE		MSAF	PROPHYLACTIC		NO ROP		
30	B/O PALANIAMMAL	29	1.5	F	LSCS	TWIN		NNJ/RDS		THERAPEUTIC	NO ROP		
31	POTHUMPONNU	33	1.8	M	NVD	SINGLE		NNJ/RDS		THERAPEUTIC	NO ROP		
32	B/O SASIPRIYA	32	1.04	F	NVD	SINGLE	BOM		PROPHYLACTIC			MILD ROP	
33	B/O NATHIYA	30	1.35	M	LSCS	SINGLE		HIE/RDS		THERAPEUTIC		MILD ROP	
34	B/O KANAGA	33	1.90	F	LSCS	SINGLE	PPROM	MSAF	PROPHYLACTIC		NO ROP		
35	B/OPORSELVI	28	1.73	F	NVD	TWIN		HIE/RDS		THERAPEUTIC			SEVI RO
36	B/O PRIYA	31	1.6	F	NVD	SINGLE		RDS		THERAPEUTIC	NO ROP		
37	B/O SELVI	29	1.01	F	NVD	SINGLE		RDS	PROPHYLACTIC				SEVI RO

38	B/O BUVANEESHWARI	30	0.97	M	NVD	SINGLE			PROPHYLACTIC				SEVI RC
39	B/O SHYAMALA	32	1.6	M	LSCS	TWIN		RDS/SEPSIS		THERAPEUTIC	MILD ROP		
40	B/O PRIYADARSHINI	30	1.2	F	NVD	TWIN		RDS		THERAPEUTIC	NO ROP		
41	B/OPRIYADASHINI	30	1.32	F	LSCS	TWIN		RDS		THERAPEUTIC	NO ROP		
42	B/O SARANYA	32	1.73	M	NVD	SINGLE		MSAF		THERAPEUTIC			SEVI RC
43	B/O MEENA	32	1.70	M	NVD	TWIN		NNJ	PROPHYLACTIC		NO ROP		
44	B/O MEENA	32	1.70	M	NVD	TWIN		NNJ	PROPHYLACTIC		NO ROP		
45	B/O PETCHIYAMMAL	29	1.20	F	LSCS	SINGLE	ANEMIA		PROPHYLACTIC		NO ROP		
46	B/O AMSAVALLI	33	1.79	F	NVD	SINGLE		RDS		THERAPEUTIC		MILD ROP	
47	B/O VARALAXMI	33	1.75	M	NVD	TWIN		RDS		THERAPEUTIC	NO ROP		
48	B/O KAVITHA	28	1.40	F	NVD	TWIN			PROPHYLACTIC			MILD ROP	
49	B/O PONNU	30	1.20	M	NVD	SINGLE			PROPHYLACTIC		NO ROP		
50	B/O ANNAM	33	1.74	F	LSCS	SINGLE	PIH	RDS		THERAPEUTIC		MILD ROP	
51	B/O FRANSIS MARY	30	1.6	M	NVD	SINGLE		RDS/MSAF		THERAPEUTIC		MILD ROP	
52	DHARSHINI	28	1.20	F	LSCS	SINGLE		RDS	PROPHYLACTIC		NO ROP		
53	B/O BANU	30	1.50	F	NVD	TWIN	PIH		PROPHYLACTIC		NO ROP		
54	B/O MEHAR	33	1.7	M	NVD	SINGLE		NNJ		THERAPEUTIC			SEVI RC
55	B/O RESHM	33	1.72	M	NVD	SINGLE		RDS		THERAPEUTIC	NO ROP		
56	B/O PARVEEN BANU	30	1.3	M	LSCS	TWIN		RDS		THERAPEUTIC	NO ROP		
57	B/O PARVEEN BANU	30	1.32	M	LSCS	TWIN		RDS		THERAPEUTIC	NO ROP		

58	B/O THAIBU	33	1.7	M	NVD	SINGLE		PERINATAL ASPHYXIA		THERAPEUTIC	NO ROP		
59	B/O SUBHASHINI	32	1.40	F	NVD	SINGLE		IUGR	PROPHYLACTIC		NO ROP		
60	B/O SHANTHI	33	1.6	M	NVD	SINGLE		RDS		THERAPEUTIC	NO ROP		
61	B/OVILASINI	33	1.40	F	NVD	TWIN			PROPHYLACTIC		NO ROP		
62	B/O VILASHINI	33	1.30	M	NVD	TWIN			PROPHYLACTIC		NO ROP		
63	B/O RAMIYA	30	1.6	M	NVD	SINGLE		RDS		THERAPEUTIC			SEVI RC
64	B/O MUNEESWARI	32	1.25	M	NVD	SINGLE		NNJ	PROPHYLACTIC		NO ROP		
65	B/O PETCHIYAMMAL	32	1.5	F	NVD	SINGLE		PERINATAL DEPRESSION		THERAPEUTIC			SEVI RC
66	B/O MARIAMMAL	32	1.43	F	NVD	SINGLE		PERINATAL DEPRESSION		THERAPEUTIC	NO ROP		
67	B/O RAJATHI	33	1.70	F	NVD	SINGLE			PROPHYLACTIC			MILD ROP	
68	B/O MUTHULAXMI	28	1.73	M	LSCS	SINGLE		NNJ	PROPHYLACTIC		NO ROP		
69	B/O ADHILAXMI	33	1.5	F	LSCS	SINGLE		PERINATAL DEPRESSON		THERAPEUTIC		MILD ROP	
70	B/O KRISHNAVENI	31	1.33	M	LSCS	TWIN			PROPHYLACTIC		NO ROP		
71	B/O SABARI	30	1.68	M	NVD	SINGLE		NNJ		THERAPEUTIC	NO ROP		
72	B/O VIJAYALAXMI	30	1.7	F	LSCS	SINGLE		HIE		THERAPEUTIC	NO ROP		
73	B/O ARTHESWARI	33	1.50	M	NVD	SINGLE			PROPHYLACTIC		NO ROP		
74	B/O RABIYA	28	1.34	F	NVD	SINGLE		MV		THERAPEUTIC			SEVI RC
75	B/O KAMALA	33	1.60	M	LSCS	SINGLE	ECLAMPSIA		PROPHYLACTIC		NO ROP		
76	B/O NATHIRA	30	1.7	F	NVD	TWIN		MV		THERAPEUTIC	NO ROP		
77	B/O AMUTHA	31	1.51	F	NVD	SINGLE			PROPHYLACTIC			MILD	

												ROP	
78	B/O RESUMA	29	1.55	M	LSCS	SINGLE		RDS/TTN		THERAPEUTIC	NO ROP		
79	B/O DIVYA	32	1.74	M	NVD	SINGLE		BIRTH ASPYXIA		THERAPEUTIC			SEVI RC
80	B/O MALATHY	33	1.7	F	NVD	SINGLE		RDS/TTN		THERAPEUTIC	NO ROP		
81	B/O SARANYA	31	1.03	F	LSCS	SINGLE			PROPHYLACTIC		NO ROP		
82	B/O MUTHUPRIYA	32	1.6	F	NVD	SINGLE		RDS/TTN		THERAPEUTIC	NO ROP		
83	B/O PECHI	31	1.45	M	LSCS	SINGLE		RDS/MV		THERAPEUTIC			SEVI RC
84	B/O RANI	33	1.67	M	NVD	TWIN		RDS/TTN		THERAPEUTIC	NO ROP		
85	B/O MARIAMMAL	32	1.44	F	NVD	SINGLE			PROPHYLACTIC		NO ROP		
86	B/O BUVANESWARI	32	1.75	F	NVD	SINGLE		RDS		THERAPEUTIC			SEVI RC
87	B/O SANGEETHA	29	1.30	M	NVD	TWIN	PIH		PROPHYLACTIC		NO ROP		
88	B/O SUBHALAXMI	32	1.1	M	NVD	SINGLE		RDS/MV		THERAPEUTIC			SEVI RC
89	B/O MANGAYARKARASI	33	1.60	F	LSCS	SINGLE			PROPHYLACTIC		NO ROP		
90	B/O ABITHA	30	1.4	M	NVD	SINGLE	CHD	PERNATAL DEPRESSION		THERAPEUTIC		MILD ROP	
91	B/OALAGURANI	31	1.20	F	NVD	SINGLE			PROPHYLACTIC		NO ROP		
92	B/O NANDINI	29	1.20	M	LSCS	TWIN	PPROM		PROPHYLACTIC		NO ROP		
93	B/O NANDINI29	28	1.10	M	LSCS	TWIN	PPROM		PROPHYLACTIC		NO ROP		
94	B/O KARTHIGA	33	1.60	M	NVD	SINGLE	PPROM/ANTENATAL STEROIDS		PROPHYLACTIC		NO ROP		
95	B/O ATHILAXMI	33	1.3	F	NVD	SINGLE		RDS/NEC		THERAPEUTIC			SEVI RC
96	B/O RENUKA	29	1.2	M	LSCS	TWIN		RDS/SEPSIS		THERAPEUTIC			SEVI

													RC
97	B/O RENUKA	29	1.2	M	LSCS	TWIN		RDS		THERAPEUTIC	NO ROP		
98	B/O SANGEETHA	32	0.75	F	LSCS	SINGLE	PPROM		PROPHYLACTIC		NO ROP		
99	B/O SUBUKANNU	31	0.85	M	NVD	SINGLE		RDS/NEC		THERAPEUTIC	NO ROP		
100	B/O VADIVUKARASI	33	1.4	M	NVD	SINGLE	ANEMIA	RDS/MV		THERAPEUTIC	NO ROP		