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JOURNAL OF THE INDIAN MEDICAL ASSOCIATION

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Reference from book :

[2]Handin RI— Bleeding and thrombosis. In: Wilson JD, Braunwald E, Isselbacher KJ, Petersdorf RG, Martin JB, Fauci AS, *et al* editors—Harrison's Principles of Internal Medicine. Vol 1. 12th ed. New York: Mc Graw Hill Inc, 1991: 348-53.

Reference from electronic media :

[3]National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ 20.pdf (accessed Jan 24, 2005): 7-18.

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[1]International Committee of Medical Journal Editors—Uniform Requirements for Manuscripts Submitted to Biomedical Journals. *JAMA* 1997; **277:** 927-34.

Editorial

ABCs of Infertility

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Extent of the problem:

One in six couples have an unwanted delay in conception. Roughly half of these couples will conceive either spontaneously or with relatively simple advice or treatment.

Most couples presenting with a fertility problem do not have absolute infertility (that is, no chance of conception), but rather relative subfertility with a reduced chance of conception because of one or more factors in either or both partners.

Most partners with subfertility will conceive spontaneously or will be amenable to treatment, so that only 4% remain involuntarily childless. As a couple has a substantial chance of conceiving without treatment, relating the potential benefit of treatment to their chances of conceiving naturally is important to give a realistic appraisal of the added benefit offered by treatment options.

Chance of spontaneous conception:

- Conception is most likely to occur, in the first month of trying (about a 30% conception rate). The chance then falls steadily to about 5% by the end of the first year. Cumulative conception rates are around 75% after six months, 90% after a year, and 95% at two years. A reasonably high spontaneous pregnancy rate still occurs after first year of trying.
- A strong association exists between subfertility and increasing female age. The reduction in fertility is greatest in women in their late 30s and early 40s. For women aged 35-39 years, the chance of conceiving spontaneously is about half that of women aged 19-26 years.
- Duration of subfertility :

The longer a couple has to try to conceive, the smaller the chance of spontaneous conception. If the duration of subfertility is less than three years, a couple is 1.7 times more likely to conceive than couples who have been trying for longer. With unexplained subfertility of more than three years, the chances of conception occurring are about 1-3% each cycle.

- Definitions of subfertility :

Subfertility is a failure to conceive after one year of unprotected sexual intercourse.

Primary subfertility– a delay for a couple who have had no previous pregnancies.

Secondary Subfertility – a delay for a couple who have conceived previously, although the pregnancy may not have been successful (for example, miscarriage, ectopic pregnancy)

Is Subfertility getting more common ?

Fecundity rates maybe declining. However, it is difficult to separate changes in social behavior and trends delaying starting a family from other factors that might reduce the chance of conception, such as environmental factors. Several studies have reported a steady decline in mean sperm counts over the past few decades in Europe and the United States. They also reported that the incidence of testicular cancers, cryptorchidism, and hypospadias if increasing.

Major causes of subfertility :

The major causes of subfertility can be grouped broadly as ovulation disorders, male factors (which include disorders of spermatogenesis or obstruction), tubal damage, unexplained, and other causes, such as endometriosis and fibroids, the proportion of each type of subfertility varies in different studies and in different populations.

Factors affecting fertility

Increased chances of conception :

- Woman aged under 30years
- Previous pregnancy

- Less than three years trying to conceive
- Intercourse occurring during six days before ovulation, particularly two days before ovulation.
- Woman's body mass index (BMI) 20-30
- Both partners non-smokers
- Caffeine intake less than two cups coffee daily
- No use of recreational drugs.

Reduced chance of conception:

- Women aged over 35 years
- No previous pregnancy
- More than three years trying to conceive
- Intercourse incorrectly timed, not occurring within six days of ovulation
- Woman's BMI <20 or >30
- One or both partners smoke
- Caffeine intake more than two cups of coffee daily
- Regular use of recreational drugs.

The impact of subfertility

The impact of experiencing difficulty conceiving should not be underestimated for couples presenting with the problem. Many find it stressful to seek professional help for such an intimate problem and feel a sense of failure at having to do so. It is not uncommon for the problem to put a strain on the relationship which exacerbates the problem. General practitioners can provide invaluable support to couples undergoing investigation and treatment and for those faced with intractable infertility.

Preconception advice

If a couple are considering starting a family they may approach their general practitioner for advice on conceiving. Areas for discussion should include things that may improve the chances of conception or increase the chance of a successful outcome to the pregnancy (by minimizing the risk of abnormality or of pregnancy related complications for baby and mother)

Managing Subfertility

A couple presenting with a delay in conception should be dealt with sympathetically and systematically according to a locally agreed protocol of investigations. Many of these investigations can be started by the couple's general practitioner and completed in secondary care. A cooperative approach allows prompt diagnosis of the problem, after which a realistic discussion can take place about the prognosis – the couple's chance of conceiving spontaneously and of conceiving with different treatment options. Formulating a plan of action can help ease some of the distress associated with the problem.

The role of general practitioners

General practitioners are often the first contact for couples concerned about their fertility. They can offer advice and support that can alleviate anxiety. Their role includes giving general preconception advice taking a history, and starting appropriate test. They should try to see both partners together, although this may be difficult if they are registered with different practices. However, the couple should be encourages to approach the problem together and must understand that they will both need investigation. General practitioners can also ensure prompt and appropriate referral, and advise on local services available in secondary and tertiary care and local funding policies for investigations and treatment.

Editorial

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Subspecialist in Reproductive Medicine & Surgery

Affordable ART for the Masses

Assisted Reproductive Technology (ART) has revolutionized the management of couples with the problem of infertility. It has been available over the last four decades and more than 5 million babies have been born with this treatment. However, the majority of infertile couples, especially in the developing countries like India, are unable to avail such facilities.

The disparity between the demand and supply of ART is largely due to its high cost. Affordability of ART is the biggest hurdle – the main barrier in accessing treatment. Since the success rate of ART is low, repetitive attempts may be necessary to achieve a favourable treatment outcome. That escalates the cost of treatment even further and thereby majority of patients drop out after one or two attempts. Although financial burden is the main cause for ART drop out, the other reasons for not continuing with the treatment are stress, agony, physical distress, uncertainty towards outcome and loss of time.

The main strategies for cost reduction of ART are follows: (1) careful patient selection, (2) simplifying pre-treatment investigations, (3) reduction in the cost of medicine, (4) streamlining clinical and laboratory steps of treatment, (5) better usage of laboratory facilities, (6) minimizing complications of treatment, and (7) arrangement of public healthcare funds.

The selection of ART over conventional therapy is mandatory in the following cases: (1) infertile women over the age of 38 years, (2) problem of more than 5 years duration, (3) associated tubal factor, (4) advanced endometriosis, and (5) severe male factor. Fertility experts must keep in mind that conventional therapies are safer, less stressful and more affordable, but it has a lower success rate and are of no benefit in certain situations. Moreover, when early results are desirable, ART is much more cost effective than conventional therapies. Primary ART without IUI is certainly more beneficial in patients with mild male factor and unexplained infertility.

The efficacy of treatment in those women who were supposed to have IUI but converted to ART due to hyper response to ovulation induction, has suggested that mild ovarian stimulation may be sufficient in the majority of patients. Such treatment regimen with clomiphene along with small dosage of gonadotrophins plays an important role in optimization of cost effectiveness for ART. In mild ovarian stimulation protocols the oocyte yield may be lower but of better quality. There is a minimum interference to the natural selection process of good quality oocytes and lesser exposer to potentially negative effects of ovarian stimulation agents, thereby resulting in a higher proportion of euploid embryos. In addition, due to relatively lower levels of oestradiol, the problem of embryo-endometrial asynchrony may be avoided. Although, development of fewer embryos and lower pregnancy rate has been reported, the cumulative

pregnancy and live birth rates remain similar to standard ART. Mild ovarian stimulation can also reduce the incidence of OHSS which often discourages patients to come back for further treatment attempts. In modern ART protocol, the usage of antagonist, GnRH agonist trigger and freeze all embryo policy can defiantly eliminate OHSS for sure.

The efficacy and benefits of elective single embryo transfer (eSET) during ART are now well established. The cumulative success rates are comparable to multiple embryo transfers with a remarkably lower incidence of multiple pregnancy and its associated complications. Multiple pregnancies have to be avoided at all cost as it is associated with a higher incidence of preterm birth, low birth weight, handicapped child and cerebral palsy. Such complications are higher even in ART singleton pregnancies as in many cases, they start off as a twin pregnancy and become singleton with miscarriage of one embryo in early pregnancy. Hence, there is a linear relationship between the number of embryo transferred and first trimester blood loss, which is commonly associated with poor pregnancy and neonatal outcome.

It is important to provide adequate information and counselling regarding a realistic success rate of ART in each individual patient. ART success depends on following parameters: (1) age and BMI of female partner, (2) duration of infertility, (3) any previous pregnancies, (4) baseline FSH, AMH and AFC values, (5) cause of infertility, (6) number of embryos transferred, (7) quality and day of embryo transfer, (8) exclusion of anuploidy embryos, (9) endometrial thickness and appearance, and 10) subendometrial blood flow. Thus each couple should be counselled about their individual ART success rate and the need for repeating ART treatment up to six attempts.

In order to increase the acceptance of ART the clinicians must work hard to remove the prevailing myths and misconceptions among general population. Even today the general belief is that ART is only for the rich and famous. Most infertile couples try to avoid ART as the last resort without realising that an early treatment would improve the success rate tremendously. People wrongly believe that the treatment is painful and requires prolonged bed rest which has to be continued throughout pregnancy. To add to this ever-increasing list of negatives is the opinion that ART babies are born with birth defects and would need special care throughout their lives.

It is therefore desirable to remove the misconceptions about untoward side effects of ART. The practice of mild ovarian stimulation and eSET can avoid the majority of side effects of ART that are related to multiple pregnancies and OHSS. Congenital anomalies in babies following ART are not caused by the treatment itself but largely due to associated parental factors. The majority of these patients are elderly, obese, hypertensive, diabetic along with their poor egg and sperm qualities. This is supported by the fact that there is no increase in birth defects in low risk patients with a singleton pregnancy following ART.

With the availability of universal public funding for ART, there is an increase in acceptability which confirms that it is the financial burden and not misconceptions or poor expectations that deter couples to avail treatment. With such financial help even clinicians change their approach to ART using milder ovarian stimulations and eSET. This automatically results in lower OHSS and fewer multiple pregnancies. The clinical pregnancy rate is lower but the cumulative success rate is much better with the option of repeating treatment cycles without any cost burden. It is interesting to note that the medical cost per cycle is lower resulting in lesser cost per live birth. The savings of fund with the changed approach can thereby pay for extra 55% ART cycles. However, the total cost of repeated ART cycles for many more patients availing treatment in the community would definitely be much higher.

Therefore, ART can only be offered to masses by changing the mindset of personals involved (both doctors and patients) along with an altered protocol for treatment. Individualised minimum ovarian stimulation is the most important step towards success and safety of ART. Proper case selection and counselling for a realistic expectation are essential to make ART acceptable. Outcome of treatment should be considered only on the basis of cumulative outcome of up to six ART attempts. For better results, ART should not be delayed as the last option of treatment for infertile couples. Finally, many low profit private and public funded ART centres are needed to reduce the cost burden of ART for people of low socioeconomic status which forms the majority of population in a developing country like India.

Original Article

Topical heparin for infusion associated superficial thrombophlebitis : A preventive approach

Rajat Charan[1], Tushar Chaurasia[2]

Maintaining a single indwelling intravenour (IV) catheter for a long duration is limited mainly due to the development of superficial thrombophlebitis. This, we decided to evaluate the efficacy and safety of heparin sodium topical solution (1000 IU/ml) in preventing infusion associated superficial thrombophlebitis. An open label, single arm clinical study was conducted. Patients undergoing elective surgery and planned to remain in situ with intravenous cannulation for at least 48 hours indoor, period were screened for the eligibility. In 47 enrolled patients were cannulated on back of the hand with IV cannula no 18. Treatment with 6 to 8 drops of Heparin Sodium Topical Solution (1000 IU/ml) was initiated immediately after the cannulation and baseline reading followed by reading every 8 hours for the treatment period of 48 hours (total 7 doses) was recorded. Patients were observed for sign and sympotoms of phlebitis developed and Graded as per Visual Infusion Phlebitis Scale. None of the patients progressed to Grade II from baseline phlebitis Grade during the study period and no application site reaction was observed in the patients. A trend towards pervention of infusion related superficial thrombophlebiotis was observed with heparin sodium topical solution (100 IU/ml)

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Key words **: Superficial thrombophlebitis, prevention, heparin, topical, infusion, catheter.**

Intravenous cannulation is an integral part of hospital based patient management. Venous access allows the medical professionals to get blood sample, as well as infuse fluids to the patient to avoid dehydration and at the same time, providing vital nutrients, medications, chemotherapy and other transfusions etc. Venous access, at times, is also associated with adverse events not limited to extravasation, ecchymosis, hematoma, infection or phelebits, which as also reported earlier[1], may impair the quality-of-life and health of patients.

Maintaining a single indwelling intravenous (IV) catheter for a long duration is limited mainly due to the development of superficial thrombophlebitis[2], which based on severity is characterized by inflammatory reaction to its wall and adjacent tissue, followed by the development of thrombus in the lumen of the superficial vein[3]. Superficial thrombophlebitis (also referred to as thrombophlebitis) is expressed by the degree of pain, redness and the extent of abnormality and if not re-solved or treated, may complicate by extension to the deep venous system, pulmonary embolism and recurrent episodes of venous thromboembolism. Saji *et al*, re-evaluated the incidence rate of infusion associated thrombophlebitis, which is reported in literature to vary between 3.7% to 67.24%, and found a prevalence of 50% which was comparable to the rates reported at the other centers of the world[4,5].

Therapy is generally symptomatic and includes the use of analgesics, anti-inflammatory agents, exercise & ambulation, and, in some cases, local or systemic anticoagulants. Positive effects were seen on pain and the reduction in thrombus size by locally acting anti-coagulants[6]. The current standard practice for treating superficial thrombophlebitis is topical heparin application for 7 days. Heparin acts by its anti-inflammatory actions and preventing coagulation rather than lysing a formed clot. So, if topical heparin is started prophylactically, even before thrombophlebitis sets in, ie, from day 1 of intravenous cannula insertion it can prevent or postpone thrombophlebitis more effectively. Furthermore, under HIC 2(d) for NABH accreditation, monitoring and prevention of infusion associated phlebitis is recommended via adherence to safe injection and infusion practices[7].

A novel topical Quick Penetrating Solution (QPS) of heparin sodium 1000 IU/ml is marketed as Phlebotroy QPS, by Troikaa Pharmaceuticals Ltd. It contains non-aqueous and non-volatile solvents with added permeability enhancers to facilitate the permeation across the skin for desired effect. Thus, we decided to evaluate efficacy and safety of heparin sodium topical solution (1000 IU/ml) in preventing infusion associated thrombophlebitis.

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Materials and Methods

An open label, single arm clinical study was conducted after approval from Institutional Ethics Committee. The patients of either gender, aged between 18 to 65 years, undergoing elective surgery and planned to remain in situ with intravenous cannulation for at least 48 hours indoor period. were screened for the eligibility. All enrolled patients were cannulated on back of the hand with IV cannula no 18. Treatment with 6 to 8 drops of Heparin Sodium Topical Solution (1000 IU/ ml) was initiated immediately after the cannulation and baseline reading was recorded in the CRFs. Treatment was applied on the skin over the cannulated vein approximately every 8 hours for the treatment period of 48 hours (total 7 doses). Study period was of 3 days for enrolled patients and they were observed for sign and symptoms of phlebitis developed from every 08 hour till 48 hours, for phlebitis Grade as per Visual Infusion Phlebitis Scale[8] and observed for application site reaction, if any. Patient with infusion phlebitis Grade II or above, as per visual infusion phlebitis scale, will be discontinued from the study.

Efficacy endpoint was proportion of patients who developed infusion phlebitis Grade II & above during 48 hours of treatment period and mean time to reach infusion phlebitis Grade II (or above) in hours. Proportion of patients with application site reaction and incidence of each application site reaction, if any, was the safety endpoint of the study.

Results

Total 47 patients satisfied the inclusion criteria and were enrolled in the study. All enrolled patients completed the study, and were included for analysis. Out of 47 patients none of them progressed to Grade II from baseline phlebitis Grade during the study period and no application site reaction was observed in the patients. No unexpected or serious adverse events were reported during the study period.

Discussion

Superficial thrombophlebitis is a common complication in which peripheral vein is traumatized which stimulates the inflammatory responses predisposing to the development of thrombus along with pain, erythema and tenderness along the venous cord. Topical heparin is the current standard therapy for superficial thromophlebitis and its anti-coagulant activity is well reported.

The present study assessed the safety and efficacy of topical solution of heparin sodium (Phlebotroy QPS, 1000 IU/ml, manufactured by Troikaa Pharmaceuticals Ltd.) in preventing infusion-associated superficial thrombophlebitis when applied on the skin over the cannulated vein three times a day over a period of 48 hours after cannulation. Phlebotroy QPS is a novel innovative product having higher strength and quick penetration through the skin, compared to conventional gel. Efficacy and safety profile of heparin topical solution is well documented by Supe *et al*[9].

Heparin topical solution was found to have a preventive role in the development of the thrombophlebitis. Out of 47 patients none of patient had developed Grade II phlebitis from Grade 0/Grade I during the study period and hence none of the patient was discontinued during the study which signified that not a single patient had developed superficial thrombophlebitis and showed significant preventive effect in progression and development of infusion related phlebitis. Favorable results were found may be due to novel patented QPS technology used in formulation which allows higher penetration of heparin through the skin. Heparin topical solution was found to be safe and well tolerated in the patients.

Conclusion

A trend towards prevention of infusion related superficial thrombophlebitis was observed with heparin sodium topical solution (1000 IU/ml). The intervention was found to be safe and effective, and its place in clinical practice needs to be established with larger, appropriately designed clinical studies.

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Original Article

Effect of starvation times on blood glucose of mother and her full term newborn before spinal anaesthesia for elective cesarean section

Sampa Dutta Gupta[1], Sulagna Bhattacharya[2], Manjushree Ray[3], Sudeshna Bhar Kundu[4], Sunanda Maji[5], Sreyashi Sen[6], Aruna Bhattacharya[7]

Pregnant mothers awaiting elective caesarean section often have fasting times much longer than recommended due to inadvertent delay in surgery. We aimed to ascertain changes in maternal and fetal blood glucose with the duration of maternal fasting. The study population comprised of Group A (n=17) liquid fasting between 2-3 hours, and Group B (n=17) liquid fasting more than 3 hours. Maternal and fetal cord blood glucose levels, Apgar scores at 1 and 5 minutes, the need for resuscitation and its correlation with newborn blood glucose level were estimated. All data analyzed statistically. Mean duration of liquid fasting in Gr.A: 2.65hours; in Gr. B: 11.35 hours. Mean maternal capillary glucose level in Gr.A:101 mg/dl; in Gr. B: 76 mg/dl. Mean neonatal cord blood glucose level in Gr.A: 96.94 mg/dl; in Gr.B:73.76 mg/dl. Apgar score in Gr A at 1 min: 8.43 and at 5 min: 9.81; Apgar score at 1 min in Gr.:7.62 and at 5 min: 9.7. Need for resuscitation in Gr.A: 11.76%; in Gr.B: 47.05%. Heel prick capillary glucose level (needed resuscitation) in Gr. A: 62mg/dl; in Gr.B:44mg/dl. The duration of fasting has significant negative correlation with maternal (-0.76) and fetal blood glucose levels (-0.73). Strong positive correlation exists between maternal and fetal cord blood glucose levels (0.97).

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Key words **: Prolonged fasting, elective caesarean section, maternal and fetal effects, neonatal resuscitation.**

Pregnant mothers awaiting elective caesarean section (C/S) are frequently delayed and fasting time is longer than recommended. Glucose turnover in fasted pregnant women is several times greater compared to demographically matched nonpregnant women. With a brief maternal fast before elective C/S there is a more rapid fall in plasma glucose concentration, moreover this fall does not initiate fetal glucose production in normal or diabetic subjects[1].

Prolonged fasting causes distress, dehydration, biochemical imbalance and hypoglycemia especially in fetus. Newborn of starved mother manifests apnoea, cyanotic spells, hypothermia, hypotonia and poor feeding. Earlier investigation showed blood glucose of fetus and newborn at birth correlates with blood glucose of the mother and maternal hypoglycaemia can cause fetal hypoglycaemia[2]. Blood glucose values of parturient vary with time of the last meal[3]. It has been found that, the greatest incidence of hypoglycaemia is seen immediately after birth[4] and carbohydrate-rich drink reduces pre-operative discomfort in elective surgical patients[5]. Moreover injectable dextrose may precipitate fetal hypoglycemia due to more activation of fetal insulin.

A hospital audit with 32 women having elective C/S revealed that 20% of study women have a drink <4 hours before elective C/S, more than half still fast >10 hsr[6].

A guideline for the multidisciplinary team of 2005 Royal College of Nursing recommended that, intake of water up to 2 hours before induction of anaesthesia for elective surgery is safe in healthy adults, and improves patient well-being. The volume of administered fluids does not appear to have an impact on patient's residual gastric volume and pH compared to a standard fasting regimen. Therefore, patients may have water and other clear fluids up to 2 hours before induction of anaesthesia.

With this background, this study was conceptualized to ascertain changes in the maternal and fetal blood glucose in relation to the duration of fasting. The aim is to compare the blood glucose levels of the mothers, undergoing elective C/S under subarachnoid block and her new-

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born, the need for resuscitation at birth.

Objectives :

(1) Fasting duration for water and solid food will be compared between the groups.

(2) Incidence of hypoglycaemia in newborns (blood glucose <40mg/dl) at birth in each group.

(3) To correlate the blood glucose of newborn that of their mothers.

(4) Apgar score at birth in newborns.

(5) Percentage of newborns requiring resuscitation at birth.

Materials and Methods

With Institutional Ethics Committee approval and written informed consent this prospective, double blind, parallel group, study was conducted with 34 adult full term pregnant women of ASA physical status I, eligible for intake of preoperative clear fluids, according to the present recommendations by the American Society of Anesthesiologists (ASA)[7] undergoing elective C/S under subarachnoid block. All patients were put up for elective C/S following the fasting guidelines of ASA[7]. Diabetic mothers, patients on hypoglycaemic therapy, inborn metabolic errors, with infection, organ failure, abnormal mentation, dizziness, delirium, autonomic dysfunction, generalized or focal seizures, focal or general motor deficit, paralysis, hemi paresis were excluded.

Sample size calculation was done based upon anticipated correlation coefficient value of 0.5 for correlation between numbers of hours of liquid fast and maternal or cord blood glucose level. It was estimated that 29 subjects would be required in order to detect correlation at this level in the underlying population with 80% power and 5% probability of Type I error.

Following routine investigations as per ASA recommendation[8], subjects were selected on the basis of history of fasting duration with advice of standard preoperative ASA fasting Guidelines[7]. According to the liquid fasting duration, study population was divided into two groups.

Group A (n=17) subjects received preoperative isotonic clear drink between 2-3 hours and Group B (n=17) subjects received preoperative isotonic clear drink >3hours before administration of subarachnoid block.

After a detailed pre-anaesthetic assessment, intravenous access was secured using 18G intravenous cannula, all patients were premedicated with inj metoclopramide 10mg and inj ranitidine 50mg iv 10mins before subarachnoid block. All patients were preloaded with Ringer lactate infusion 10ml/kg[15] over 20mins. Monitors were applied with an automatic blood pressure (BP) cuff, ECG, and pulse-oximeter. Subarachnoid block was instituted using a 25G Whitacre needle at L3–L4 interspaces in sitting position with 0.5% hyperbaric bupivacaine 8–12 mg, thereafter patients were placed in supine position with a wedge angled 10°-15° placed under right hip to obtain a left uterine displacement. Onset of cephalad spread of analgesia was determined as loss of pin prick and block was confirmed at the level of T5-6. All patients were given O_2(3 lt/min) through nasal prongs.

Ringer Lactate 5–6 mL/kg/hour for 1hour, then 500 mL hydroxyethyl starch 6% solution were infused together until completion of surgery. In >20% decrease in systolic BP (SBP) below baseline after subarachnoid block was defined as hypotension. Hypotension was initially treated with fluid resuscitation, if not responded, inj. phenylephrine was administered IV titrated. Bradycardia (<60/min) was treated with inj atropine 0.02 mg/kg IV. Heart rate, respiratory rate, BP, SpO_2 were noted preoperatively and every 5 minutes intra-operatively.

Inj oxytocin (5–10 units) was infused slowly intravenously after delivery of baby. The APGAR scores of the newborn were recorded at 1 and 5 mins after delivery. Total duration of solid and liquid fasting time in hours was noted for each patient. Capillary blood glucose of mothers and newborn's cord blood were estimated and need of resuscitation was recorded. Blood glucose was determined by glucose oxidase method.

End Point of Study :

Primary end point: Maternal capillary and newborn cord blood glucose levels in mg/dl.

Secondary end point: Apgar score at 1min.

All data was entered into excel spreadsheet and analyzed usingStatistica version 6

Numerical data were presented as MEAN±SD and analyzed by Students t-test. Parametric data were analyzed using one way analysis of variance test (ANOVA). Fisher's exact test was used for categorical variables. All tests were two tailed. A p value of less than 0.05 was considered statistically significant.

For neonatal resuscitation, American Heart Association Care Guidelines for Neonatal Resuscitation: 2010[9] were followed. For Apgar scoring system, recording of five objective signs pertaining to the condition of infants at birth were used. Apgar at 1 minute score is of value in assessing the need for resuscitation whereas at 5 minutes was strongly considered with infant mortality and morbidity. Capillary blood glucose (mg/dl) of newborn needed resuscitation was estimated by heel prick method[10].

Results

A total 56 term pregnant women awaiting elective C/S were needed to assess to select 17 subjects for each Group. Group A with liquid fasting duration between 2-3hrs and Group Bwith liquid fasting duration >3 hours. The pie-diagram (Fig 1) shows total 56 term pregnant women (77%) awaiting elective C/S with ASA fasting guideline were needed to survey prospectively to get 17 patients (23%) for each Group. Therefore, total 34 full term pregnant women awaiting elective C/S were included in this study. There were no cases of apparent or suspected pulmonary aspiration or other drink-related complications before, during or after surgery within the study population.

Demographic profile (Table 1) revealed comparable results (p>0.05) in terms of age, sex, weight, haemodynamic parameters and gestational age between the two groups. SBP (Group A 126.2±9.3; Group B 120.3±7.27), diastolic BP (Group A. 80.7±8.2; Group B. 77.62±5.62), Heart rate (Group A 104.29±14.2; Group B 92.33±9.62) before the induction of subarachnoid block were insignificant.

Table 2 shows, difference in categorical variables between the groups were done by fisher's exact test. Analysis reveals11.76% of neonates born to mothers in Group A neded resuscitation whereas 47.05 % of neonates born to mothers in Group B required resuscitation. Fisher's exact test shows a p value <0.05 which is statistically significant.

Table 1 and Fig 2 show correlation between blood glucose of neonates and mothers – 0.97 (Pearson's correlation coefficient r) (p<0.05). Comparison of fasting duration in hours for solid and liquid in groups (mean±SD) was done in Table 5, which revealed that in Group A duration of liquid and solid fasting corroborates where fasting guidelines were strictly followed. But in Group B duration of both solid and liquid fasting is prolonged. This indicates that in Group B, due to procedural delay, had prolonged fasting periods (for both solid and liquid), inspite of standard fasting advice.

Table 1 shows gestational age, birth weight and 1 min Apgar score distribution of infants in the different fasting groups. Analysis reveals that, the difference between Apgar at 1min in Group A and Group B is statistically significant. The difference between need for resuscitation in Group A and Group B is statistically significant.

Fig 3 shows point biserial correlation coefficient. Cor-

Table 1 — *Demographic profile (mean ±SD). Comparison of fasting duration in hours for solid and liquid in both groups: (mean ± SD),gestational age, birth weight and 1 min apgar score distribution of infants in the different fasting groups, Comparison of apgar score, heart rate ,respiratory rate,colour, maternal blood glucose level and neonatal blood glucose level, blood glucose level of the newborns who required resuscitation between the groups (mean ± SD).*

Characteristics	Group A (n = 17)	Group B (n =17)	P value
Age (year) (mother)	25.24±2.22	24.32±2.36	>0.05
Weight (kg) (mother)	58.38±2.	55.19± 1.02	>0.05
Height(cm) (mother)	151.02±1.13	149.242± 2.32	>0.05
Gestational age(wk) (mother)	37.18±3.2	38.12± 2.45	>0.05
Hb% (mother)	12.35±2.14	14.29 ± 1.42	>0.05
Urea mg/dl (mother)	27.71±3.18	26.39 ± 1.84	>0.05
Creatinine mg/dl (mother)	0.82±0.14	0.80±.53	>0.05
Prothrombin time (sec) (mother)	13.2 ±1.22	12.2±0. 22	> 0.05.
SBP (mmHg) Pre op. (mother)	126.2±9.3	120.3±7.27	>0.05
DBP (mmHg) Pre op. (mother)	80.7±8.2	77.62±5.62	>0.05
Volume preload (ml) (mother)	793±23.42	780±25.24	>0.05
Heart rate /min (mother)	104.29± 14.22	92.33±9.62	>0.05
Fasting time (hrs)	6.63±2.07	14.3±5.42	<0.05
Solid(mean±SD)	(5.53-7.74)	(11.5-17.1)*	
Fasting time(hrs) liquid	2.65±0.31	11.35±3.21	<0.05
(mean±S.D)	(5.53-7.74)	(9.74-12.96)*	
Birth weight (Newborn) (mean±SD)	2.78±0.22	2.71±0.20	
1min Apgor score			
(mean±SD)(Newborn)	8.43±1.63	7.625±1.644	<0.05
Need for resuscitation	(2)	(8)	<0.05
(Newborn)	11.76%	47.05%	
Apgar at 1 minute	8.43?1.63	7.625±1.644	<0.05
Apgar at 5 minutes	9.8125 ?0.13	9.705±0.187	> 0.05
Need for resuscitation	(2)/ 17	(8)/ 17	<0.05
	11.76%	47.05%	
Neonates with Heart rate at birth >100;100-60; <60 /min	17:0:0	17:0:0	>0.05
Respiratory rate at birth apnoea/ labored	Labored 2	Labored 8	>0.05
No of neonates with peripheral cyanosis	1/17	6/17	< 0.05
No of neonates with central cyanosis	0	0	--
Cord blood glucose level at birth(mg/dl)	98.0000 (R= 43.000)	74.58824 (R=60.000)	0.000113*
blood glucose of Newborn (mg/dl) needed resuscitation (mean±SD)	(2)/17 81.5±9.192	(8)/17 57.5±5.928	<0.05
Hypoglycemia in newborn	0 /17	0 /17	

*p<0.05=Statistically significant. p>0.05=statistically not significant.

Table 1 shows Demographic profile (age, sex, weight), haemodynamic parameters, gestational age were comparable (p> 0.05) between the two groups. Systolic arterial blood pressure (SBP) (Group A. 126.2±9.3; Group B 120.3±7.27), diastolic blood pressure (DBP) (Group A. 80.7±8.2; Group B. 77.62± 5.62) and values before the induction of subarachnoid block were comparable (p>0.05). Heart rate (baseline) before the induction of subarachnoid block was not statistically significant between the groups (Group A 104.29± 14.2 Group B 92.33± 9.62).

Comparison of fasting duration in hours for solid and liquid in both groups: (mean ± SD), shows that in Group A duration of liquid fasting corroborates with duration of solid fasting where fasting guidelines were strictly followed. But in Group B duration of both solid and liquid fasting is prolonged. This indicates that in Group B due to procedural delay had prolonged fasting periods (for both solid and liquid) inspite of standard fasting advice.

Gestational age, birth weight and i min apgar score distribution of infants in the different fasting groups shows that, the difference between Apgar scores at 1min in Group A and Group B is statistically significant. The difference in the need for resuscitation in Group A and Group B is statistically significant.

Comparison of apgar score, heart rate,respiratory rate,colour,blood glucose level in new born needed resuscitation between the groups analysed by *Mann Whitney U test, and shows a significant difference between the two groups in terms of Apgar at 1 minute, Need for resuscitation, No of neonates with peripheral cyanosis, Cord blood glucose level at birth(mg/dl) and blood glucose of Newborn (mg/dl) needed resuscitation (mean±SD)

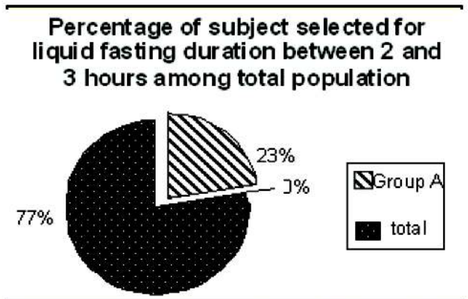

Fig 1— A total of fifty six term pregnant women (77%) was required to get seventeen patients (23%) for Group A and seventeen patients (23%) for Group B for this study. Therefore, a total of thirty four term pregnant women awaiting elective C/S were assessed for study eligibility to meet the inclusion criteria.

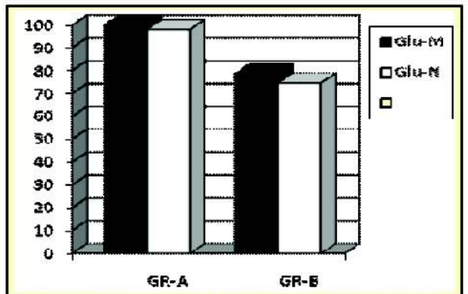

Fig 2 — Comparison between blood glucose of infants at birth and mother at delivery by cesarean section. Correlation of maternal blood glucose level with fetal cord blood – 0.97 (pearson's correlation coefficient r) ($p<0.05$)

GLU-M: maternal mean blood glucose level
GLU-C: neonatal blood glucose level
GR-A: group-A GR-B: group-B

relation between glucose levels and need for resuscitation, correlation with maternal glucose level (–0.38)which is significantly negatively correlated ($p< 0.05$) and with cord blood glucose level (–0.34)(significant at $p< 0.05$). Fig 4 shows correlation of newborn blood glucose level compared to that of their mothers at delivery(mg/dl). Fig 4 shows correlation of newborn blood glucose level compared to that of their mothers at delivery (mg/dl).

Table 1 shows comparison of Apgar score heart rate, respiratory rate, cord blood glucose level in newborn needed resuscitation between the groups, analysis reveals the difference between the 2 groups in terms of Apgar score at 1 minute, need for resuscitation of newborns, number of neonates with peripheral cyanosis, cord blood glucose level at birth (mg/dl) blood glucose of newborn (mg/dl) needed resuscitation (mean±SD).

Discussion

This prospective double blind study revealed that, despite maintaining standard ASA fasting guideline[7] in patients for elective C/S, the duration of fasting time got prolonged (Mean duration of liquid fasting in Gr.A: 2.65hrs; in Gr.B: 11.35 hours). The incidence of patients maintaining recommended duration of fasting is only 23% which was revealed during the selection of study population (Fig 1). This finding is consistent with the study of RS Ikonen, E Hagman and P Pystynen where they revealed 49% of parturient fasted for 6-12 hours, 38% for 12-18 hours and 13% found fasted over 18 hours[1].

No definite correlation is established yet related to the duration of fasting at which maternal blood glucose level is responsible for declines in fetal blood glucose level below cut-off point (40mg/dl). In the present study, the decrease in maternal (-0.76)and cord blood glucose (-0.73)

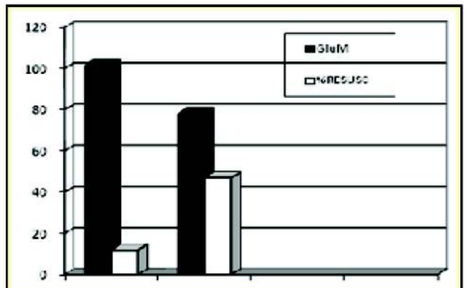

Fig 3 — Comparison between maternal blood glucose levels and need for resuscitation (point biserial correlation coefficient)

With maternal glucose level – 0.38(significant at $p< 0.05$)
With cord blood glucose level –0.34(significant at $p< 0.05$)
GluM- maternal blood glucose level
%RESUSC: % of neonates requiring resuscitation
GR-A: group-A GR-B: group-B

Table 2 — *Difference in categorical variables between the groups – fisher's exact test*

	Group	Resuscitation Not needed	Resuscitation Needed	Row Totals
Count	A	15	2	17
Row Percent		88.23%	11.76%	
Count	B	9	8	17
Row Percent		52.94%	47.05%	
Count	All Groups	23	10	34

Table 2 shows, 11.76% of neonates born to mothers in Group A needed resuscitation whereas 47.05 % of neonates born to mothers in Group B required resuscitation. Fisher's exact test shows a p value <0.05 which is statistically significant.

In the decades after the publication of Mendelson's data, the series of triennial confidential reports on maternal death in the United Kingdom highlighted the initial importance of nothing per oral and policies were rapidly introduced. Maternal fasting leads to more rapid decline in blood glucose and rapid lipolysis, fetus can use ketones derived from the mother as alternative fuels for oxidation in situation of glucose deprivation.

were correlated significantly in opposite direction with duration of fasting ($P<0.05$) signify that, glucose turnover in fasted, pregnant women is many folds greater compared to demographically matched nonpregnant women (Table 2). Moreover this result was similar to the study of Spellacy, WN, Suhi, WC, Bradley, B & Holsinger, KK[2]. This study also revealed the existence of strong positive correlation between maternal blood glucose level and fetal cord blood glucose level (Tables 2&3) similar to another study of Phillips, L, Lumley, J, Paterson, P and Wood, C[11].

A low Apgar score on the one-minute test reflects neonatal requirements of medical attention[12]. Apgar at 1 and 5min in this study (Fig 2) showed a positive significant correlation (0.58) which reflects the need for resuscitation. The concept of hypoglycaemia in the newborn has changed in recent years and the classification has been revised[4]. Similar to the study of Cutberlet, RL and Cornblalth, this study also showed the development of greatest incidence of hypoglycaemia immediately after birth[4,13,14].

Newborns with lower blood glucose levels are at increased risk for brain injury. Increased glucose levels after hypoxia or ischemia were not associated with adverse effects in a recent pediatric series[17]. Intravenous glucose infusion should be considered as soon as possible after resuscitation, with the goal of avoiding hypoglycemia (Class IIb, LOE C).

The present study justifies the above reason (Table 1) as 8 newborns who needed resuscitation in Group B were born with labored breathing with heart rate >100, the incidence of blood glucose level revealed from heel prick capillary test about (57.5±5.928) mg/dl in the prolonged fasting group in comparison to (81.5±9.192) mg/dl in the strictly followed liquid fasting group (Group A). Though they have not crossed the cutoff point of hypoglycaemia (<40 mg/dl), but the newborns required resuscitation followed by immediate dextrose infusion. Neonates of starved mothers need resuscitation with serum glucose level <40-45 mg/dl, either with oral feeding (2-3 mL/kgD10 in water) or by intravenous infusion dextrose 8mg/ kg/minute[9].

Discomfort during the period of waiting before elective surgery can be reduced if patients are prepared with an isotonic health drink, compared to oral water or overnight fasting.The volume of administered fluids does not appear to have an impact on patient's residual gastric volume and pH,compared to standard fasting regimen. Therefore, patients may have unlimited volume of water and other clear fluid up to 2 hours before induction of anaesthesia[7].

Conclusion :

To overcome problems related to inadvertent procedural delay for elective

C/S, parturients may be encouraged to drink isotonic glucose containing drink upto 2-3 hours before surgery for birth of a healthy newborn as strong positive correlation revealed between solid fasting with maternal blood glucose level, in addition, maternal and fetal cord blood glucose level again significantly correlated with need for neonatal resuscitation.

Limitation :

The betahydroxybuterate concentration in maternal and cord blood was not assessed, which is suggested a simple diffusion from mother to fetus to use as alternative fuels for oxidation in situation of glucose deprivation.

Conflict of Interest : Nil

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Original Article

Effectiveness and safety of drotaverine hydrochloride on first stage of cervical dilatation and in labor pain management — A Meta-analysis

JB Sharma[1], P Vanamail[2]

Labor is a complex process that involves many factors such as myometrial contraction, cervical ripening, dilatation and the expulsion of the fetus and placenta. Prolonged labor increases the incidence of maternal distress, PPH, birth canal injury and puerperal sepsis. Fetus is also exposed to higher risk of infection, asphyxia, intracranial stress and increased incidence of operative delivery. Therefore, providing relief from labor pain and shortening duration of labor is a challenge for obstetricians. There are various agents now in use as smooth muscle relaxants which inhibit spasm that impairs cervical dilatation. They include hyoscine,valethamate bromide and drotaverine hydrochloride. The purpose of the meta-analysis was to assess efficacy, safety and potency of drotaverine hydrochloride in terms of duration of first stage of labor, incidence of cervical tears, maternal and fetal outcomes and cervical dilatation rate. Literature search was made using inclusion and exclusion criteria and comprehensive meta-analysis was carried out. All the studies carried out in comparing the efficacy of drotaverine and valethamate consistently showed that there is a significant decrease in first stage labor, pain duration and a significant increase in cervical dilatation rate with drotaverine as compared to valethamate. Drotaverine has definitely proven to be superior in shortening the duration of first stage of labor and significantly increases cervical dilatation rate as compared tovalethamate bromide thus providing a convenient, shorter, physiological and uncomplicated delivery without any adverse effects on maternal and neonatal outcome.

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Key words **: Labor, Cervical dilatation, Spasmolytic, Drotaverine, Valethamate, Meta-analysis.**

Agony and stress experienced by women due to labor pain is beyond description. Shortened duration, reduction of pain in labor and early return to the routine activity are cherished dreams of every woman in labor and also desired by the majority of obstetricians. Prolonged labor pain leads to increased incidence of maternal distress, which is one of the causes for the incidence of operative delivery[1]. The most common cause of prolongation of first stage of labor is cervical spasm leading to cervical dystocia[2]. Effacement and subsequent dilatations of the cervix are markers of the progress and duration of labor. Progress of labor is assessed by progressive dilatation of the cervix and progressive descent of presenting part[3]. It has been proven that the cervical dilatation is one of the important factors, which determines the duration of labor and uterine activity. The dilatation stage has a variable time course determined by the initial stage of the uterine orifice, the intensity of labor pains, constitutional characteristics of the parturient and by the fact, whether parturient is a primipara or multipara.Inhibitory impulses in the form of spasm often impair the dilatation of cervix and prolong the duration of labor despite good uterine contractions[2].

Providing pain relief during labor reduces maternal stress and results in shortening of labor with improved maternal and fetal outcome during delivery. Many clinical trials have been carried out on the acceleration of labor to prevent the risks of prolonged labor such as maternal exhaustion, infection, dehydration and ketoacidosis. Since all these causes increase physiological burden for the mother, these events may eventually cause complications in the second stage of labor and puerperium. Thus a short firststage of the labor is naturally of dual advantage for both obstetricians and pregnant women[4].

Ideal pharmacological agent for management of labor :

An ideal pharmacological agent should help in dilatation and effacement of cervix thereby shortening the duration of first stage of labor without interfering with myometrium activity, second and third stage of labor; with no harmful effects to mother and fetus. Commonly used pharmacological agents in the management of labor are tranquilizers or prostaglandins, which are associated with harmful effects on both mother and fetus. Anticholinergic agents like hyoscine and valethamate bromide are also used but these have side effects like dry mouth, tachycardia, blurred vision etc, and are contraindicated in women with glaucoma, severe hypertension, paralytic ileus and ulcerative colitis. Most commonly used agent is drotaverine hydrochloride, which is an isoquinoline derivative having a powerful spasmolytic action on smooth muscle cells. Drotaverine acts through PDE-IV inhibition having PDE-IV isoenzyme selectivity, calcium blocking effect, low anti-aggregatory effect and sodium channel antagonistic effect. Further, drotaverinelacks cardio toxic effect due to its PDE IV isoenzyme selectivity, sodium channel antagonistic effect and calcium channel antagonistic effect[5]. Therefore, an attempt has been made to analyze the results of drotaverine from various studies in terms of efficacy, safety and potency against comparators using comprehensive meta-analyses.

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Materials and Methods

Literature search was made using following inclusion and exclusion criteria —

Inclusion criteria :

(a) Randomized trials of comparative studies of drotaverine in the management of labor.

(b) Regular established uterine contractions at the rate of at least two contractions per 10 minutes, each contraction lasting for at least 40-45 seconds.

Exclusion criteria :

(a) Induced labor.

(b) If any spasmolytic agent had been used within 48 hours.

As per the inclusion and exclusion criteria, eligible studies published in bibliographic electronic databases such as MEDLINE, EMBASE, CINAHL and LILACS were searched up to March 2015. Eligible studies were analyzed on the following clinical endpoints:

(a) duration of first stage of labor

(b)incidence of cervical tears

(c) maternal and fetal outcomes and

(d) cervical dilatation rate.

Meta-analysis methods :

Meta-analysis was performed in two stages. In the first stage measures of treatment effect with its 95% confidence interval (CI) was calculated for each individual study. In the second stage an overall treatment effect was calculated as a weighted (inverse of the variance of the treatment effect) average of the individual summary statistics. Treatment effect of mean scores were assessed by standardized mean difference (SMD), which was calculated based on study size, mean score and level of significance. For a dichotomous outcome measure the treatment effect was assessed based on odds ratio (OR) and Mantel-Haenszelrisk ratio.

Since each study was carried out with different samples, the sampling error variability is likely to be high in a meta-analysis. The other source of heterogeneity might be due to characteristics of the samples, variations in the treatment, in the design quality and so on. Therefore, assessing the heterogeneity in meta-analysis is a crucial issue because the presence versus the absence of true heterogeneity (between studies variability) canaffect the statistical model. The presence of true heterogeneity has been tested using Q test, which follows a chi-square distribution with k–1 degrees of freedom, k being the number of studies. When not rejecting the homogeneity hypothesis a fixed-effects model was adopted. However, the strength of the Q statistic depends on the number of studies that will be included in the meta-analysis. Therefore, I^2index obtained by dividing the difference between the result of the Q test and its degrees of freedom by the Qvalue itself was also used in percentage values along with Tau-square, which indicates the degree of heterogeneity. Comprehensive meta-analysis software (evaluation version), which incorporated all the above statistical procedures was used for the present meta-analysis. Studies with at least 25 subjects were included for analysis and for statistical significance $P<0.05$ was considered. The treatment effect and its 95% CI of each study and over effect were shown in forest plots.

Ethics : The Nature of manuscript is based on Meta-analysis from the published articles. Therefore, the issue of ethics doesn't arise.

Results

Duration of first stage of labor:A total of 18 randomized studies were identified as per the inclusion and exclusion criteria. The mean duration (minutes) of first stage of labor was available for 15 studies (Table 1). Out of these 15 studies 12were carried out with drotaverine drug (Group

Table 1 — *Clinical studies on drotaverine and its role in reduction in duration of 'first stage of labor*

Studies	No. of Subjects	Mean duration of first stage labor (in minutes)		
		Drotaverine(n)	Valethamate(n)	Control(n)
NagariaT*et al*[4]	200	113.5 (100)	177.4 (100)	-
Roy A*et al*[6]	200	148.9 (100)	-	331.6 (100)
Singh KC *et al*	100	265.4 (44)	-	312.3 (40)
Pai MV *et al*[7]	281	156 (141)	-	222 (140)
Sharma JB *et al*[1]	150	194 (50)	220 (50)	412.8 (50)
Sankar M *et al*[8]	300	174.5 (100)	196 (100)	344.7 (100)
Poornima RR *et al*[9]	200	190 (100)	-	250 (100)
Kaur D *et al*[2]	300	116 (250)	158 (50)	-
Mishra SL *et al*[10]	150	205 (50)	275 (50)	373 (50)
JayashreeS *et al*[13]	200	123.1 (100)	160 (100)	-
Dahal P *et al*[14]	300	178.3 (100)	254.3 (100)	346.3 (100)
Ibrahim MI *et al*[15]	352	120.7 (176)	-	200.8 (176)
Demeter J *et al*[16]	200	183.6 (100)	-	236.2 (100)
Kalhon P *et al*[19]	100	331.4 (50)	-	145.1 (50)
Ashraf S *et al*[20]	450	179.1 (150)	198.6 (150)	299.0 (150)

A) involving 1,161subjects with drotaverine drug (Group A) and 1,156 subjects with control (Group B). All the above trials had shown that the 'duration of first stage of labor' was significantly lower (P value <0.05) in the patients who were given drotaverine compared to control group.Meta-analysis was carried out using these 12 studies results by assuming that all the studies had similar effect with similar kind of study subjects (Fixed effect model). The forest plot of meta-analysis is shown in Fig 1. All the studies showed that there was a significant (P value <0.05) decrease in pain score due to drotaverine as compared to control. The overall effect size (95% C.I) for favoring the drotaverine is estimated to be 0.283 (95%C.I: 0.201-0.365) and it is statistically significant (Z=6.78; P value <0.001).Heterogeneity test (Tau-square=0.00, Chi-square=2.38;df=11; P value=0.997; I2=0) indicate that there is no heterogeneity among the studies and confirming that the fixed effect assumption is valid. The conclusion is that all the studies consistently showed a significant decrease in pain duration due to drotaverine drug compared to control group.

A total of eight studies (Table 1) were conducted in comparing the efficacy of drotaverine (Group A) with that of valethamate (Group B) involving 900 and 700 subjects in the respective drug groups. The forest plot of meta-analysis is depicted in Fig 2 and the treatment effect of all the trials were found to be statistically significant (P<0.05).

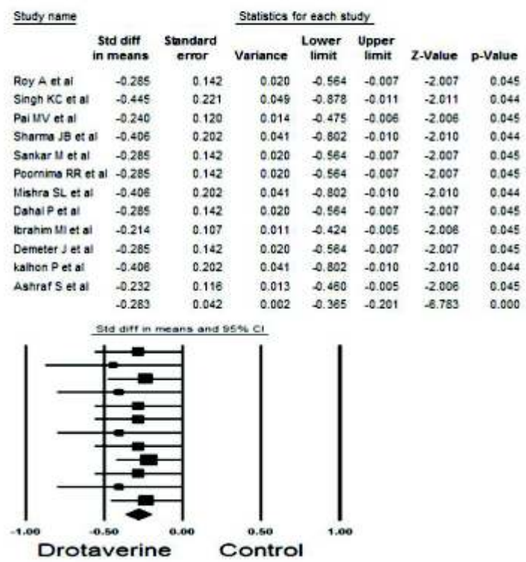

Fig 1 — Impact of Drotaverine drugs on duration of first stage labor compared to control

The overall effect size (95% CI) favoring the drotaverine drug was estimated to be 0.294 (95%C.I: 0.191-0.397) and it is statistically significant (Z=5.60;P value <0.001). Heterogeneity test (Tau-square=0.00, Chi-square=0.93; df=7; P value=0.996; I^2=0) indicate that there is no heterogeneity among the studies and the conclusion is that all the studies consistently showed a significant decrease in pain duration due to drotaverine compared to valethamate.

Incidence of cervical tears (%): A total of seven studies (Table 2) were carried out in comparing the incidence of cervical tears due to drotaverine (Group A) with that of control (Group B) involving 716 subjects in each drug groups. The forest plot of meta-analysis is shown in Fig 3 and the treatment effect of individual study results showed that only one study (Demeter J, *et al*) differed significantly between the drotaverine drug and control. However, the overall effect size (95% C.I) 0.102 (95%C.I: 0.053-0.198) favoring the drotaverine drug was found to be significant (Z=6.80; P value =0.000). Heterogeneity test (Tau-square=2.93, Chi-square=19.83; df=6; P value =0.003; I^2=69.73) indicated that there was a heterogeneity among the studies. However, while fitting random effect model the overall effect size (95% C.I) 0.232 (95% C.I: 0.048-1.115) was not statistically significant (P>0.05). The conclusion is that even though individual study results (except one) did not show significant difference, the overall effect size derived from fixed effect model showed a significant decrease in cervical tears incidence rate due to drotaverine compared to control group.

Out of four studies, which reported incidence of cervical tears for both drotaverine (Group A) and valethamate (Group B), two studies showed zero incidence in both the drug groups. Based on the remaining two studies involving 210 subjects in each group forest plot of meta-analysis is shown in Figure 4.The overall effect size (95% CI) for favoring the drotaverine drug was estimated to be 0.246 (95% CI: 0.027-2.22) and it is not statistically significant (Z=1.25; P=0.212). The conclusion is that there is no strong evidence to state that the cervical tears incidence rate due to drotaverine is significantly less as compared to valethamate.

Maternal and fetal outcome: All mothers who received drotaverine injection gave birth to babies having APGAR score of 8-10 for about 90% of children compared to comparator(s), which had also recorded almost similar score (Table 3). Therefore, meta-analysis for APGAR score could not be carried out due to the fact that in more than 90% of study subjects treated with either of the drugs (drotaverine/valethamate) or acted as control, the APGAR score was shown to be between 8 and 10 in

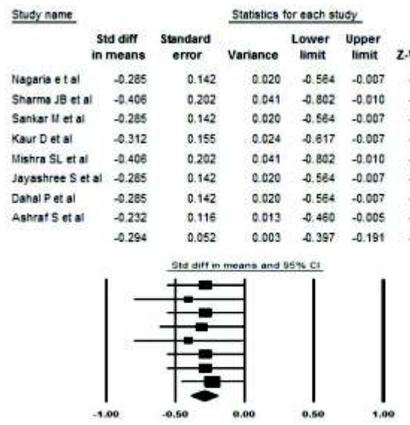

Fig 2 — Impact of Drotaverine and Valethamate drugs on duration of first stage labor

majority of the studies. Further, based on range of values of APGAR score no meaningful meta-analysis could be carried out.

Cervical dilatation rates (%) : Out of 13 clinical studies (Table 4) only seven were found to be eligible for meta-analysis in comparing the cervical dilation rates (%) between drotaverine (group A) and control (group B) involving 625 and 624 study subjects in the respective drug groups. The forest plot of meta-analysis is shown in Fig 5 and all the seven studies showed a significant (P value <0.05) increase in cervical dilatation rate due to drotaverine compared to control. The overall effect size (95% C.I) for favoring the drotaverine drug was estimated to be 0.291 (95%C.I: 0.179-0.403) and it is statistically significant (Z=5.11; P value =0.001).Heterogeneity test (Tau-square=0.00, Chi-square=2.09; df=6;P value =0.910; I^2=0) indicated that there is a homogeneity among the studies and the conclusion is that all the studies are consistently showing the significant increase in cervical dilatation rate due to drotaverine as compared to control.

A total of 10 studies (Table 4) reported cervical dilatation rate for both drotaverine (Group A) and valethamate (Group B) involving 1,009 and 809 study subjects in the respective drug groups. The forest plot of meta-analysis is shown in Fig 6. The overall effect size (95% CI) for favoring the drotaverine drug was 0.305 (95%C.I: 0.209-0.401) and statistically significant (Z=6.23; P value =0.001). Heterogeneity test (Tau-square=0.00, Chi-square=1.53; df=9; P value =0.99; I^2=0) indicated that there is no heterogeneity among the studies and the conclusion is that all the studies are consistently showing the significant increase in cervical dilatation rate due to drotaverineas compared to valethamate.

Discussion

Labor is a multifactorial process, which involves myometrial contraction, cervical ripening, dilatation and the expulsion of the fetus and placenta. Providing relief from labor pain is always a challenge for gynecologists and obstetricians. Shortening of labor pain results in improved maternal and fetal outcome because in prolonged labor, the incidence of maternal distress (dehydration, ketoacidosis), PPH, birth canal injury and puerperal sepsis are more with resultant increase in maternal morbidity. Fetus is also exposed to higher risk of infection, asphyxia, intracranial stress (due to excessive cranial moulding) and increased incidence of operative delivery[1]. There are various agents now in use as smooth muscle relaxants, which inhibit spasm that impairs cervical dilatation. They include anticholinergic agents like hyoscine, valethamate bromide, and directly acting antispasmodics like drotaverine hydrochloride. The anticholinergic agents have side effects like dry mouth, tachycardia, blurred vision etc, and are contraindicated in women with glaucoma, severe hypertension, para-

Table 2 — *Clinical studies on Incidence of cervical tears*

Studies	Incidence of cervical tears (%)		
	Drotaverine (n)	Valethamate (n)	Control (n)
Pai MV *et al*[7]	0.7 (140)	-	2.3 (140)
Roy A *et al*[8]	Reduced incidence (100)	- (100)	
Mishra SL *et al*[10]	0 (50)	0 (50)	2 (50)
Sankar M *et al*[6]	0 (100)	0 (100)	2 (100)
Poornima RR *et al*[9]	1 (100)	-	1 (100)
Jayashree S *et al*[13]	0 (100)	1 (100)	-
Ibrahim MI *et al*[15]	1.9 (176)	-	1.3 (176)
Demeter J *et al*[16]	3 (100)	-	61 (100)
Ghosh A[17]	0 (110)	2 (110)	-
Kalhon P *et al*[19]	0 (50)		8 (50)

Table 3 — *Clinical studies on APGAR Score of new born babies*

Studies	APGAR Score (at 5 minutes)		
	Drotaverine	Valethamate	Control
Pai MV *et al*[7]	9 for 99.25%, 8 for 0.75 %, <8 none (141)	-	9 for 96.80 % and 8 for 2.34 %, <8 for 0.78 % (140)
Mishra SL *et al*[10]	8/10 for 100 % (50)	8/10 for 98 % (50)	8/10 for 98 % (50)
Sankar M *et al*[6]	7-10 for 98 % (100)	7-10 for 92 % (100)	7-10 for 92 % (100)
Poornima RR *et al*[9]	6-8 in 4% and 8-10 in 88% (100)	-	6-8 for 4% and 8-10 for 88% (100)
Nagaria T *et al*[4]	9.76 (100)	9.63 (100)	-
Singh KC *et al*[18]	9.96 (44)	-	9.93 (40)
Palii SB *et al*[12]	8-10 in 92% (50)	8-10 in 86% (50)	-
Ibrahim MI *et al*[15]	9 (176)	-	9 (176)
Demeter J *et al*[16]	9.68 (100)	-	9.32 (100)
Ashraf S *et al*[20]	9.1 (150)	9.2 (150)	9.2 (150)

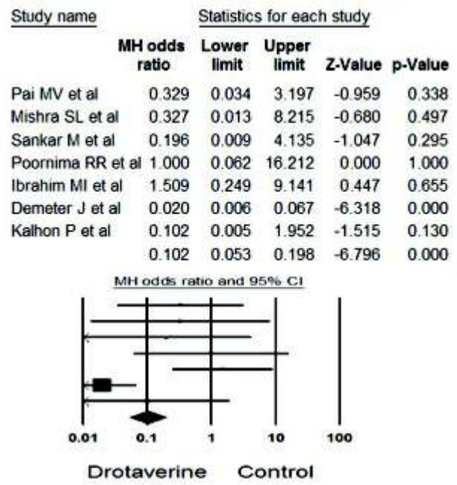

Fig 3 — Impact of Drotaverine drug on incidence of cervical tears (%) compared to control

lytic ileus and ulcerative colitis.

Smooth muscle constitutes approximately 10% of the cervix[21] which forms the physiological background for the use of various smooth muscle relaxants in the stage of dilation of labor to produce good effect on the consistency and dilation of cervix.Blasko found that type IV Phosphodiesterase (PDE) enzyme is present in increased concentration in the third trimester in myometrium, suggesting its contribution in regulating uterine motility. Drotaverine, a well-established therapeutic agent that directly acts on smooth muscles through selective inhibition of phosphodiesterase-IV isoenzyme may help to facilitate dilatation of cervix and is free from anticholinergic side effects. It is a superior smooth muscle relaxant which acts specifically

Table 4 —*Clinical studies on role of drotaverine on 'cervical dilatation'*

Studies	Cervical dilatation rates (cm/h)		
	Drotaverine	Valethamate	Control
Madhu C *et al*[11]	3 (49)	2.4 (49)	1.9 (48)
Nagaria T *et al*19	3.3 (100)	2.1 (100)	-
Sharma JB *et al*[1]	2.04 (50)	1.87 (50)	1 (50)
Kaur D *et al*[12]	3.99 (250)	2.74 (50)	
Singh KC *et al*[18]	1.2 (44)	-	-
SankarM *et al*[8]	2.71 (100)	2.39 (100)	1.35 (100)
Mishra SL *et al*[10]	2.05 (50)	1.53 (50)	1.13 (50)
Palii SB *et al*[12]	1.92 (50)	1.44 (50)	-
Jayashree S *et al*[13]	3.31 (100)	2.58 (100)	-
Ibrahim MI *et al*[15]	2.7 (176)	-	1.8 (176)
Ghosh A[17]	3.45 (110)	1.3 (110)	-
Kalhon P *et al*[19]	2.3 (50)	-	1.3 (50)
Ashraf S *et al*[20]	2.6 (150)	2.3 (150)	2.0 (150)

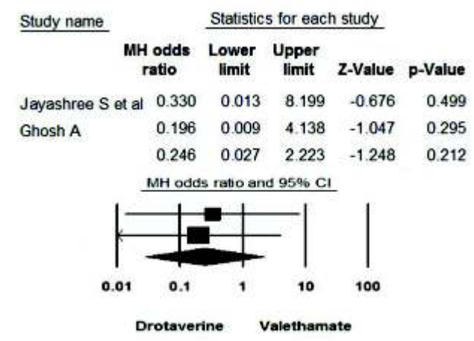

Fig 4 — Impact of Drotaverine and Valethamate drugs on incidence of cervical tears (%)

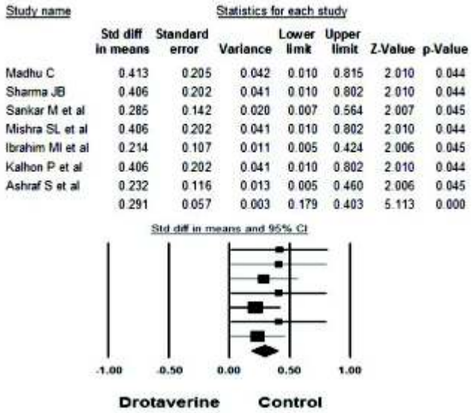

Fig 5 — Impact of Drotaverine drug on cervical dilation compared to control

on spastic sites and corrects the cAMP and calcium balance relieving smooth muscle spasm.This inhibitory action is detectable only in lower uterine segment during labor since muscle fibers in upper uterine segment are strongly affected by contractile effect of oxytocin. It acts by increasing the intracellular concentration of substrate camp, which produces cervical dilatation. The smooth muscle cone of the uterine cervix which remains normally contracted during pregnancy till early labor, starts relaxing near term when cervix is taken up. Once contraction sets in, this cone is situated above the equator of the fetal head. This pulling up process requires adequate relaxation of the smooth muscle cells of muscle cone. Dilatation of the smooth muscle cone helps the rest of the ground sub-

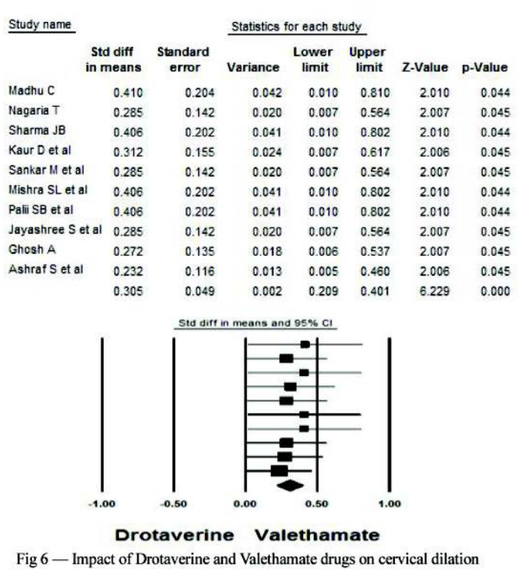

Fig 6 — Impact of Drotaverine and Valethamate drugs on cervical dilation

stance of the cervix to respond to uterine contractions. Use of drotaverine during pregnancy is free of any teratogenic and embryotoxic effects[4].

The use of drotaverine in the first stage of labor for hastening cervical dilatation, reducing duration of labor and consequently providing significant pain relief is well established by various trials done in India and internationally. Further, in one of the studies[7] carried out in India the effect of drotaverine is more in multigravida than in primigravida. Thus, due to its efficacy and safety drotaverine is widely used in first stage of labor for cervical dilatation and labor pain management, which is safe for mother as well as fetus. In the present meta-analysis it has been established that all the studies consistently showed a significant treatment effect in favor of drotaverineas compared to valethamate and control group. In addition to reduction in duration of first stage of labor, drotaverine is found to be promising candidate in increasing the dilatation rate that is essential for uncomplicated pregnancies. All mothers who received drotaverine injection gave birth to babies having APGAR score of 8-10 for about 90% of children compared to comparator(s), which had also recorded almost similar scores. Further, the combined study results suggested that drotaverine significantly ($P<0.05$) reduces the incidence of cervical tears.

Conclusion

Around 20 clinical trial studies with more than 3900 women have concluded that drotaverine has definitely proven to be superior in shortening the duration of first stage of labor and significantly increase cervical dilatation rate as compared to valethamate bromide and hyoscine thus providing a convenient, shorter, physiological and uncomplicated delivery without any adverse effects on maternal and neonatal outcome. It does not cause fetal asphyxia. Drotaverine is free from fetal and maternal anticholinergic side effects which are commonly seen with anticholinergic agents like hyoscine and valethamate bromide and it is a safe drug to augment labor, resulting in better maternal and fetal outcome as compared to comparator(s). Hence drotaverine can be used as first line of drug for cervical dilatation and augmentation of labor.

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Competing interest : The authors do not have any conflict of interest in publishing this article.

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Authors' contribution : JB Sharma conceptualized the idea, collected data for meta-analysis and wrote the manuscript. P.Vanamail carried out meta-analysis, incorporated the statistical aspects and involved in writing the manuscript. Both the authors have read and approve the final version of the manuscript.

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Original Article

Oral Betamethasone-azathioprine pulse : a patient compliant modification of Dexamethasone — cyclophosphamide pulse therapy for pemphigus

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Pemphigus vulgaris (PV) is an autoimmune vesicobullous disorder in India with a very high mortality rate (>90%) if untreated. 1Immunosuprresives are the mainstay of treatment. Dexamethasone-cyclophosphamide pulse (DCP) therapy has also gained popularity in early remission in these patients. But it has also got some disadvantages. So we have modified the therapy with oral betamethasone and azathioprine. (1)To reduces loss of working hours of patients by giving a therapy requiring minimum hospital stay. (2) Reducing side effects and cost of DCP therapy. (3) Keeping the effectiveness of treatment at par with DCP therapy. A prospective, randomized study was carried out in a tertiary care setting in Kolkata among sixty - seven consecutive patients of pemphigus vulgaris & foliaceous attending the Dermatology OPD from February 2008 to December 2010. Like the original DCP therapy in our study also we have four phases. The first phase of remission in this study is for 12 months, the main changes being — (1) Use of oral betamethasone instead of injectable dexamethasone, (2) Use of azathioprine as steroid sparing drug instead of cyclophosphamide, (3) Home therapy for the last 6 pulses of phase.

Sixty two patients completed the study; out of them 27 were males and 35 females. Forty eight patients achieved remission in 3 pulses, 7 patients needed up to 6 pulses and 7 patients needed more than 6 pulses (up to 17 pulses) to achieve remission. Recovery was noticed as early as one week in cutaneous lesions and 2 weeks in mucous lesions. Regular patients achieved remission early. Betamethasone Azathioprine Pulse Therapy is more acceptable to the pemphigus patients due to its flexibility regarding hospital attendance. It is cheaper, and at the same time it is at par in affectivity to other modalities of pulse therapy like DCP with lesser or same side effects.

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Key words **: Oral betamethasone, azathioprine, pulse therapy, pemphigus vulgaris, compliance.**

Pemphigus vulgaris (PV) is a relatively common autoimmune vesicobullous disorder in India with a very high mortality rate[1]. Although the worldwide incidence of pemphigus has been reported to be in the elderly (more than 50 years), Sehgal[2] observed 50% of pemphigus in north India occurred between 21 and 40 years of age. Studies from North India have reported a higher incidence of pemphigus in patients from poor socioeconomic strata[3-5].

The prognosis of PV has dramatically improved with the use of systemic corticosteroids and various anti-inflammatory and immunosuppressive agents. However, prolonged daily therapy that is required to achieve a good control of PV is associated with several distressing side-effects. Pulse therapy (administration of a supra-pharmacological dose of a drug over a short period at a fixed interval) initiated with the aim of completely suppressing the cyclical proliferation of immunocompetent cells, gave a new vision to the treatment of pemphigus[2]. Since the advent of the fixed dose, fixed duration regimen of dexamethasone-cyclophosphamide pulse (DCP) with daily oral cyclophosphamide for PV in India in 1983 and its subsequent modification (addition of daily oral steroid in the initial stage in very active cases), long-term remissions have been reported in large case series of patients[6,11]. The efficacy of DCP regimen in management of pemphigus has been reported time and again. This concept of pulse therapy has virtually revolutionized the treatment of pemphigus by providing faster control, longer remission and providing the concept of "cure" in pemphigus, which was unknown previously[4,7,8,9].

Although side effects are common, DCP is one of the mainstays of treatment of pemphigus in India[4]. However this therapy has some drawbacks like:

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(1) Three days of hospital stay each month is a prolonged period where day-care facilities are lacking.

(2) Cyclophosphamide is contraindicated in the child bearing period.

(3) Last of all, cost of therapy is relatively high for a developing country.

Keeping these issues in mind, we propose oral betamethasone azathioprine (BAP) pulse in the treatment of PV, as an alternative to DCP regimen. The main changes being— (1) Use of oral betamethasone instead of injectable dexamethasone. (2) Use of azathioprine as steroid sparing drug instead of cyclophosphamide. (3) Home therapy for the last 6 pulses of phase II.

Aims and objectives: (1)To reduce loss of working hours of patients by giving a therapy requiring minimum hospital stay. (2) To reduce side effects and cost of DCP therapy. (3) To keep the effectiveness of treatment at par with DCP therapy.

Materials and Methods

This was a prospective, randomized study carried out in a tertiary care setting in Kolkata. Sixty - seven consecutive patients of pemphigus vulgaris & foliaceous attending the Dermatology OPD from February 2008 to December 2010 were enrolled.

Inclusion criteria : All consecutive patients with pemphigus vulgaris and foliaceous who expressed consent after information.

Exclusion criteria : (1) Patients above >65years and <12 years. (2) Patients with preexisting hypertension, renal failure, pregnancy & lactation, psychiatric disorders, uncontrolled diabetes, active tuberculosis, ischemic heart disease with or without chest pain, dyselectrolytemia.

Evaluation of the patients : All patients were examined thoroughly. Investigations included complete blood count, blood urea, sugar-fasting and post prandial (PP), glycosylated Hb (HbA_{1C}), serum Na^+ & K^+, SGOT, SGPT, bilirubin, electrocardiogram (ECG), sputum for AFB, chest X-Ray and urine for routine and microscopic examination. Specific investigations like Tzanck smear, skin biopsy for routine staining and for direct immunoflourescence test (DIF) were also done.

Schedule of home administered pulse:

Tablet pantoprazole (40 mg) along with domperidone was administered early in the morning.

One Hundred tablets of betamethasone (1mg) were dissolved in a glass of water. This was taken orally sip by sip for 3-4 hours daily along with 3-4 bananas. This schedule was followed for 3 consecutive days. Patients with history of dyspepsia were advised to take two teaspoon of antacid gel in addition.

Later on, keeping compliance and comfort issues in mind, we modified the schedule as: 30, 30 and 40 tablets of betamethasone 1 mg dissolved in each glass of water and consumed consecutively with one banana for each glass in three hours (one glass in one hour) along with liquid antacid. We called this as steroid cocktail. Patients were given 12 such pulses after they went into remission. Azathioprine was administered 50 mg daily (arbitrarily chosen) for eighteen months and then stopped. Patients were followed up for eighteen months thereafter.

Blood pressure, ECG, serum Na^+, K^+, fasting blood sugar and urine for routine and microscopic examination were monitored every month.

Pulses were administered under direct supervision till six pulses after remission. For last six month patients took pulse at home at predetermined dates and reported to us day-before and day-after, provided there were no serious side-effects. Twelve consecutive pulses were given after patient went into remission. Additional daily doses of prednisolone (0.3-0.5 mg/kg) were continued till remission and tapered off. Diabetic patients were given oral hypoglycemic and/ or insulin as per endocrinologist's advice.

To look for hypothalamic-adreno-cortical axis suppression, we estimated early morning serum cortisol in patients selected in a randomized manner.

Results

Duration of disease at presentation varied from 2 months to 2 years with only cutaneous lesions in 9 pts, only mucosal in 2 pts and muco-cutaneous in 54 patients, respectively (Table 1.).

Sixty two patients completed the study; out of them 27 were males and 35 females. Forty eight patients achieved remission in 3 pulses, 7 patients needed up to 6 pulses and 7 patients needed more than 6 pulses (up to 17 pulses) to achieve remission. Recovery was noticed as early as one week in cutaneous lesions and 2 weeks in mucous lesions. It was also noticed that regular patients achieved remission early (Fig 1).

Patients who had delay in subsidence of the initial lesion or who had extensive lesions in the beginning, additional daily oral betamethasone 2 -3 mg /day given. Patients, who had relapse in phase III and IV again put in BAP therapy(Table 2).

Side-effects were seen in 18 (29%) patients (Table 3,4,5). Major side-effects were gastrointestinal and sleep related which were managed with increasing antacid and h2 blocker and sedatives as required. Infections, fungal, bacterial and viral were treated accordingly. Although some of them were extensive but we didn't face any problem to control them.

Discussion

At this moment, when dexamethasone and cyclophosphamide in different permutation and combination showed very good results for the management of pemphigus vulgaris[10-13,6] (Table 1), we thought some other type of corticosteroid and non-corticosteroid immunosuppressant to manage some specific problems.

Table 1 — *Showing Duration of Disease*

Age group of patients treated	Number of patients	Male	Female	Attended regularly	Attended irregularly	Reason for irregularity
Upto 30 yrs	8/11.94%	3	5	8/100%		
30 –45 yrs	42/62.68%	17	24	39/92.85%	3	Occupational
45 -65 yrs	17/25.37%	8	9	15/88.23%	2	Not known
Total	67	29	38	62	5 (3/2)	

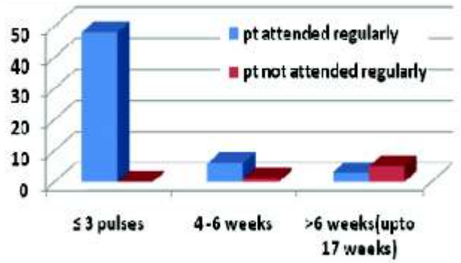


Fig 1 — Response to treatment, duration of phase one

Table 2 — *Status of patients at the end of the study*

Remission	Non- compliant, Left out from study	Death phase III	Relapse in phase IV	Relapse in
62	4(3 + 1)	1	9	4

Why betamethasone? The target of this study was to modify the management of pemphigus patients with pulse therapy as such that patient can self- administer the therapy in such a convenient place and technique , so that it will help him to lose less working days and earning, without compromising the quality of the therapy . Betamethasone can be taken orally. The comparison with other systemic glucocorticoids is as follows.

For several decades, dermatologists have utilized azathioprine to treat numerous debilitating skin diseases. This synthetic purine analog is derived from 6-mercaptopurine. It is thought to act by disrupting nucleic acid synthesis and has recently been found to interfere with T-cell activation. The most recognized uses of azathioprine in dermatology are for immunobullous diseases, generalized eczematous disorders, and photodermatoses[14] . The most common side effects of azathioprine includes nausea and vomiting, sometimes accompanied by abdominal pain or diarrhea. Less often, azathioprine may cause hepatitis , pancreatitis or an allergic reaction that may include a flu-like illness or a rash and leucopenia.

Pasricha and Poonam6 treated 123 patients over a 5-year study period with modified pulse regimen. The modifications over standard DCP pulse incorporated use of oral betamethasone on tapering doses according to disease severity in phase 1 with the result of significant shortening of the phase 1. As the plasma half life of Betamethasone is significantly more than dexamethasone (300 minutes in comparison to 200 minutes of dexamethasone), we thought the possibility of less interpulse relapse in this study, and it also helped to design our study. Our studies showed that less number of patients needed daily corticosteroid in the form of daily oral betamethasone in the first phase, and also for shorter duration. This benefit may be due to the same reason of longer half life of betamethasone.

The left out rate in pulse therapy is very high. Reason behind the lack of patient compliance are various, but after perusal of many studies (Table 7), it was obvious to us that, regular hospital admission is one of the most important reason, loss of work hours and cost of therapy (Table 8) inclusive of hospital admission charges was a factor.

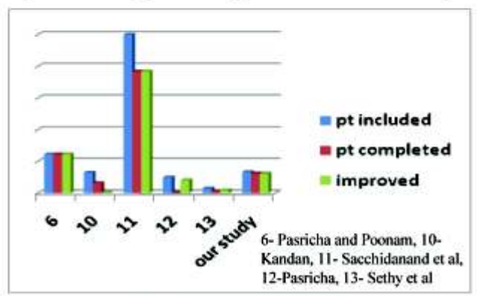
Table 3 — *Immediate side effects during phase I*

Adverse effects	No of patients (n=62)
Anorexia	13
Nausea /Dyspepsia	11/7
Insomnia /mood changes/anxiety	9/2/3
Myalgia/weakness after pulse	9/2
Hypertension/ palpitation/chest pain/epigastric pain	4/2/1/4
Headache/blurred vision/ urticaria/ pedal edema	2/1/2/2
Cough/ dyspnoea	5/2

Table 4 — *Delayed side effects in phase II/III*

Adverse effects	No of patients (n=62)
Oral candidial infection / dermatophytosis/ furunculosis	11/5/3
Obesity/cushingoid features	16/18
Hypertension/hyperglycemia	3/9
Oligomenorrhoea/ amenorrhoea	11(29 females of premenopausal age)
Osteopenia/cataract/DVT/ diffuse scalp hair loss	3/2/1/3
Eczema Herpeticum / Acne/pneumonia	1/4/2

It has been observed that those patients who were regular in their pulses required less number of pulses to go into clinical remission[15]. In our study majority of patients went into remission in as early as 3 months, all of them were regular in taking pulse therapy. Cutaneous lesions disap-



6- Pasricha and Poonam, 10- Kandan, 11- Sacchidanand et al, 12-Pasricha, 13- Sethy et al

Fig – 2 Types of pulses with result

peared faster than mucous lesions.

Pulse therapy is extremely safe regarding side effects. The AIIMS experience[11] showed that there is no risk of increase bodyweight, or development of diabetes or hypertension, peptic ulceration, osteoporosis, striae, acne, hirsutism or other side effects commonly associated with corticosteroids unless the patient was receiving or had received conventional daily doses of corticosteroids, side effects associated with cyclophosphamide were also generally very infrequent. Leukopenia, thrombocytopenia and anemia were rarely seen also hemorrhagic cystitis and generalized hyperpigmentation, major side effects of cyclophosphamide were diffuse hair loss, amenorrhoea, azoospermia. Side effects were more in the first phase of the regimen when daily corticosteroids in addition to pulse were given. Other studies[4,6,13,15] on DCP were also had significantly less side effects. In comparison to other studies our studies also has remarkably less and minor side effects.

Table 7 — *Reason behind left out from study*

Study Reference number	Number of patients Included	Number of patients completed	Left out in different stage	Reason
11	500	384	97	(+19 died)
Pasricha JS				
6	143	123	17	not known
Pasricha JS, Poonam				
13	28	25	3	Went abroad, stopped
Sethy PK *et al*				
4	300	227	61 (12 died)	Various reasons
Pasricha JS, Khaitan BK, Raman RS				
10	65	33(phase 1)	14	Male-work related
Kandan S, Thappa DM.				/financial; Female- family reason, financial.
15	54	58%		Frequent hospitalisation High cost
Mahajan VK, Sharma NL, Sharma RC, Garg G.				
17	41	34	7	not known
Rao PN, Laksmi TS.				
This study	67	62	4	Shifted far-away, stopped own, not known.

During the initial stages of this therapy, we were in dilemma how patients would tolerate it, particularly gastritis and its response to control the dreaded disease. As our target was to allow the patients to take few pulses in there home, we evaluated every patients before starting, during taking and after completing the pulse to look for side effects. The side effects in BAT pulse were insignificant, infrequent and random, and also in comparison to other type of pulse it was not much. Major side-effects were gastro-intestinal, gastritis being the commonest. Initially, patients were complaining of that, so we divided in 30, 30 and 40 tablets of betamethasone in each glass of water and mixed with liquid antacid and was taken with fruit juice or banana. These combinations were tolerated by the patients better. We named it Steroid Cocktail. The risk of increased pyogenic infections on the skin, and candidiasis of the mouth persisted only as long as the patient had ulcers on the skin and oral cavity, and therefore adequate treatment with standard systemic antibiotics and antifungal agents during this period was enough and very helpful. No side effects of azathioprine were noted. Amongst almost half of the patients pituitary-adrenal function was found to be suppressed 1 month after the last pulse of phase II but, all these patients were asymptomatic and remained well during subsequent follow up[18].

Table 8 — *Expenditure per pulse*

DCP	BAP
Rs 650/ per pulse excluding mid cycle pulse, and daily cyclophosphamide, oral prednisolone	Rs 150/ pulse excluding daily azathioprin,, and daily oral prednisolone.

Table 5 — *Side-effects detected (*n = 62*) in investigations*

	No of patients
Chest X-ray(pneumonitic changes)	2
Anaemia leucocytosis/leucopenia	13/24/5
Pyuria/albuminuria	13/6
Raised urea/creatinine /liver enzymes/blood sugar	
Serum cortisol(less)	4/1/9

Table 6 — *Comparison between Hydrocortisone and other glucocorticosteroid*

	Potency relative to Hydrocortisone			Half-Life	
	Equivalent Glucocorticoid Dose (mg)	Ante inflammatory	Mineral corticoid	Plasma (minutes)	duration of action (hours)
Intermediate Acting :					
Prednisolone	5	4	0.8	200	12-36
Methylprednisolone	4	5	0.5	180	12-36
Long Acting :					
Dexamethasone	0.75	30	0	200	36-54
Betamethasone	0.6	30	0	300	36-54

Reference : Adrenal Cortical Steroids. In Drug Facts and Comparisons. 5th ed. St. Louis, Facts and Comparisons, Inc.:122-128, 1997

Conclusion

We concluded that, Betamethasone Azathioprine Pulse Therapy is more acceptable to the pemphigus patients due to its flexibility regarding hospital attendance. It is cheaper, and at the same time it is at par in affectivity to other modalities of pulse therapy like DCP with lesser or similar side effects. Work hours are not lost and patient compliance was better. It also provides as a new armamentarium in the fight against pemphigus.. However, initial counseling is required to convince patients of taking 100 tablets a day. We also suggest STEROID COCKTAIL a new way to circumvent gastritis associated with pulse therapy.

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Observational Study

Dermatoscopic evaluation of nail changes in psoriasis

Manjulata Dash[1], Sambit Ranjan Dalei[2], Tanmay Padhi[3], Subhasree Madhual[4]

Dermatoscopy is a newer modality of investigation to evaluate nail changes. The present study was conducted to assess the patterns of nail changes in patients of psoriasis by dermatoscope and to differentiate psoriatic nail changes and other nail disorders. Prevalence of nail changes was found to be 10.22% among all cases of psoriasis. Male agricultural workers in their fifth decade were commonly affected. Chronic plaque psoriasis was the most common clinical type of psoriasis seen in 74.69% followed by scalp psoriasis in 6.79%. Hypertension and diabetes mellitus were observed in 37.65% and 20.37% of cases respectively. Nail bed changes were the most frequently encountered seen in 89.51% followed by nail matrix changes (74.69%). Out of all nail bed changes, onycholysis was the most common morphological defect visible to naked eye (69.92%) whereas splinter hemorrhage was the most common change visible by dermatoscope (75.86%). Pitting was the most common change observed both by naked eye and dermatoscope.

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Key words **: Psoriasis, nail changes, dermatoscopy.**

Psoriasis is a chronic, recurrent, immune mediated inflammatory skin disease which affects about 1.5-3% of the world's population with an apparently equal sex incidence[1,2]. Various genetic components and several environmental factors like infections are postulated to play important roles in the different types of presentation of the disease, most commonly as chronic, symmetrical, erythematous, scaly papules and plaques[3].

Lifetime incidence of nail involvement in psoriatic patients is estimated to be 80-90%,being common in the males and in the persons with higher bodyweight[4,5]. Concurrent nail psoriasis is seen inapproximately 10-78% of patients with cutaneous psoriasis, while 5-10% of patients having isolated nail involvement without any skin lesions[6-9].

The involvement of nails is frequent in psoriasis and the clinical spectrum is very heterogeneous depending on the involvement of the nail bed, matrix or folds[10]. Nail matrix involvement leads to coarse nail pitting (most common finding of nail psoriasis), dystrophy of nail and leukonychia. Nail bed alterations are onycholysis, subungual hyperkeratosis, splinter hemorrhages, oil drop/salmon patches, thickening of nail plate, whereas nail fold involvement results in paronychia. Combined nail matrix and nail bed psoriasis may develop psoriatic crumbly nail[11]. Psoriatic nails constitute a risk factor for secondary mycotic infections, which can occur in up to 27% of the cases[12].

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Nail psoriasis is thought to be associated with severe form of skin involvement and prolonged duration of skin lesions.

Nail dermatoscopy is a recent modality of investigation for the diagnosis of nail disorders being performed with hand held or video dermatoscope. Both clinical as well as dermatoscopic findings in nail psoriasis depend on the part of the nail unit affected.The nail matrix characteristics include pitting, longitudinal or transverse ridges and nail plate crumbling and characteristic nail bed changes are onycholysis, salmon patch and splinter hemorrhages[13].

Although nail psoriasis affects a substantial proportion of psoriasis patients and causes significant psychological distress, few epidemiologic data characterizing patients with nail involvement are available.Nevertheless, insufficient studies are available to validate use of a dermatoscope and a lack of evidence to recommend it as an alternative or substitute for nail biopsy.

Aims & Objectives :

The study objective was

- To assess the patterns of nail changes in patients of psoriasis both by naked eye and a dermatoscope
- To visualize subtle nail changes and to differentiate psoriatic nail changes and other nail disorders

Materials and Methods

It was a hospital based cross-sectional study conducted from October 2014 to October 2016 where all patients clinically diagnosed with psoriasis with nail changes attributable to psoriasis attending the OPD and indoor were included.

Patients who had received any systemic treatment for psoriasis for at least one month before enrollment and those under any other treatment inducing or aggravating psoriasis were excluded from the study.

Detailed history regarding demographic details such as (age, sex, educational status, socioeconomic status), duration of skin and nail involvement, family history of psoriatic nail changes and presence of any other co morbidities other than psoriasis were recorded.

All cases enrolled into the study were subjected to clinical examination as general examination,Body mass index (BMI),Systemic examination,Dermatological examination-included assessment of type and severity of psoriasis according to psoriasis area and severity index (PASI).

Nails were examined both by naked eye and with a dermatoscope and Nail Psoriasis Severity Index was calculated.

Observation

In the present study, 1589 patients had psoriasis, out of 54607 patients who visited the OPD during the study period, making the prevalence of psoriasis up to 2.91%.

The prevalence of nail involvement among 1589 psoriasis patients was calculated to be 10.22% as 162 patients were found to have some degree of changes in nails attributable to psoriasis and were included in the study as cases.

In our study, majority of patients were male 94(58.03%) outnumbering females, with male: female ratio of 1.38: 1(94/68) (Table 1).

Table 1 — *Age Distribution of Cases*

Age (in years)	No of cases	Percentage
0 – 10	5	3.08
11 – 20	11	6.79
21 – 30	19	11.72
31 – 40	28	17.28
41 – 50	51	31.48
51 – 60	32	19.75
>60	16	9.87

Most of the patients were in the age group 41-60 years (51.23%). Mean and median ages were found to be 43.41±14.82 years and 46 years respectively.

Out of 162 patients, 99(61.11%) patients hailed from urban area and 63(38.89%) patients from rural areas (Table 2).

Table 2 — *Occupation, Educational & Socio Economic Status*

	No of Cases	Percentage
Occupation :		
Farmer	47	29.01
Office worker	31	19.14
Housewife	34	20.99
Businessman	29	17.9
Unemployed	21	12.96
Educational Status :		
Illiterate	13	8.02
Primary	37	22.84
Secondary	63	38.89
Higher	49	30.25
Socio-economic Status :		
Lower	19	11.73
Upper Lower	33	20.37
Lower middle	47	29.01
Upper middle	41	25.31
Upper	22	13.58

Among various occupations, farmers comprised of 47(29.01%) significant number of cases followed by housewives 34(20.99%) and office workers 31(19.14%). Majority of patients 63(38.89%) had studied up to secondary level while 49(30.25%) had completed graduation or above. Majority of patients 47(29.01%) belonged to lower middle socio-economic group. 41(25.31%) patients had upper middle and 33(20.37%) had upper lower status (Table 3).

Table 3 — *Clinicaltypes of Psoriasis*

Sl no	No of cases	Percentage
Chronic plaque	121	74.69
Erythrodermic	9	5.55
Isolated Scalp psoriasis	11	6.79
Guttate	7	4.32
Inverse psoriasis	5	3.09
Isolated nail psoriasis	9	5.55

Amidst different morphological patterns of psoriasis, patients of chronic plaque psoriasis 121(74.69%) constituted highest number followed by scalp psoriasis 11 (6.79%) and psoriatic erythroderma, isolated nail psoriasis 9(5.55%) each.

Mean duration of skin involvement and nail involvement were found to be 20.21±11.04 years and 13.97±10.59 years respectively. Similarly median durations were of 21years and 15 years respectively. Out of total 162 patients, 31(19.13%) patients had family history of psoriasis with nail involvement (Tables 4 & 5).

Table 4 — *PASI and Nail Changes*

PASI	No of Cases	Percentage
<10	31	20.26
10 – 20	90	58.82
>20	32	20.91

Out of all cases, 61(37.65%) were hypertensive, 37(22.84%) patients had deranged lipid profile while 33(20.37%) showed having DM. Other co-morbidities were found in the form of dermotophytic skin infections, chronic kidney disease, lichen planus and chronic obstructive pulmonary disease.

Table 5 — *Showing Co-morbidities*

Types of Diseases	No of Cases	Percentage
DM	33	20.37
HTN	61	37.65
Hyperlipidaemia	37	22.84
CKD	04	02.46
Lichen planus	03	1.85
Dermatophytic skin infection	13	8.02
COPD	07	4.32

Out of 162 people who were included in the study, diagnosis of psoriatic changes of nail was made of only with the help of a dermatoscope in 29(17.9%) cases while in rest the changes were visible by naked eye.

While only finger nails were involved in 32(19.75%) patients, exclusively toe nail involvement was seen in 19(11.72%) patients (Table 6).

In our study, majority of patients 61(37.65%) had up to 6 -10 number of nails involved followed by 47(29.01%) of cases who had involvement of more than 10 number of nails.

Table 6 — *Number of Nails Involved*

No of Nails Involved	No of Cases	Percentage
1	22	13.58
2-5	32	19.75
6- 10	61	37.65
>10	47	29.01

Out of 162 patients enrolled in the study, nail bed involvement was seen in maximum number of cases which is 145(89.51%) followed by nail matrix and nail fold changes which were 121(74.69%) and 31(19.13%) respectively (Table 7).

Table 7 — *Nail Changes*

Nailbed changes	visible to naked eye	visible in dermatoscope	Nailmatrix changes	visible in naked eye	visible to dermatoscope
Subungual hyperkeratosis	41	7	Pitting	83	19
Onycholysis	93	18	Leukonychia	28	14
Splinter hemorrhage	37	22	Red spots	25	11
Salmon patch	29	19	Crumbling	71	02

Onycholysis in 93(69.92%) was found to be the frequently visible nail bed changes to the naked eye. Subungal hyperkeratosis was seen in 41(30.82%) and salmon patch in 29(21.81%)

When nail bed changes were visualized through a dermatoscope splinter haemorrhages were the most common in 22(75.86%) cases amidst the other nail bed changes.

In the current study, pitting was seen in 83(62.41%) cases making it the commonest nail matrix change, visible to naked eye followed by crumbling of nail, which was observed in 71(53.38%) cases.

Pitting in form of micro pits was the distinct nail matrix change observed by a dermatoscope in 19(65.51%) cases followed by leukonychia in 14(48.27%) cases (Table 8).

Table 8 — *Showing NAPSI*

NAPSI	No of Cases	Percentage
<40	126	77.77
40 – 80	33	20.37
81 – 120	3	1.85
>120	0	0.00

NAPSI value, being the most common tool to assess severity of nail changes when used in our study up to 126(77.77%) cases had values in between 0 to 40 (Table 9).

Table 9 — *Presence of other Concurrent Nail Diseases*

Other Nail Diseases	No of Cases	Percentage
Onychomycosis	69	42.59
Traumatic oncholysis	39	24.07
Pterygium	11	06.79
Others	3	1.85

Onychomycosis in 69(42.59%) cases, traumatic oncholysis in 39(24.07%) cases were the commonest nail diseases which were simultaneously present with the psoriatic nails.

Symptoms of psoriatic arthritis were evident in 33(20.37%) patients, while in rest of the patients, any history of such symptoms could not be traced out.

Discussion

Psoriasis is a chronic, noncontagious inflammatory disease with variable morphology, distribution, severity, and course.Its prevalence was estimated to be approximately 2-3% as observed by Schon P *et al* in 2005 and Gudjonsson JE *et al* in 2006 which was comparable in our present study of prevalence being 2.91%[14,15]. However various Indian studies conducted by Bedi in 1977 and Kaur I et al in 1986 found the prevalence to be 0.8% and 1.4% respectively which assumably could be due to small sample size[16,17].

Various authors like Calvert HT *et al* in 1963, de Jong EM *et al* in 1996, Salomon J *et al* in 2003 had proposed the nail involvement in psoriasis cases could be 10 to 78%[6-8]. In our study the prevalence of nail involvement was found to be 10.19%. A German study by Augustin M *et al* in 2010 with a larger sample size of 3531 psoriasis patients found prevalence of nail involvement to be 40.9%[18].

Out of 162 cases of psoriasis patients with nail changes in our study, 94(58.03%) were males and 68(41.97%) were females. Therefore, a male preponderance was observed which is in accordance with the result of German study conducted by Augustin M *et al* (64.33% male), Malaysian study by Yap FB *et al* (Male 61.3%) in 2010[18,19]. However Schons KR *et al* in 2015 in his study observed a slight female preponderance[20]. Psoriasis is believed to be an immunologically mediated disorder with equal sex distribution and a higher incidence in males possibly reflects the trend in health seeking behavior in developing countries like India.

In our study, mean and median ages were calculated to be 43.41±14.82 years and 46 years respectively. The findings are quite proportionate to the results obtained by Klaassen KM *et al* in 2014 in Netherland (mean age 51.5±15.0 years) and Schons KR *et al* in 2015(mean age 51.8±15 years)[20,21]. Most of the cases belonged to 41-50 years age group (51 patients) in our study which could be attributed to increase economic independence and ability to spend on healthcare during that decade.

As far as the locality distribution of the cases concerned, 99(61.11%) patients hailed from urban area while 63(38.89%) patients from rural areas. This could be due to more stress, sedentary lifestyle with unhealthy addictions and also more treatment aspiring behaviour in urban people.

In a Brazilian study, Schons KR *et al* in 2015 in plaque psoriasis patients with nail changes observed farmers comprising 33.8% of cases followed by housekeepers 16.9% and sellers 10.7%[20]. Similarly in our study, farmers comprised of 29.01% cases followed by housewives 20.99%, office workers 19.14% and businessmen 17.9%. This could be due to ethnic, economic and geographic difference between two countries.

Out of 162 cases, 13(8.02%) were found to be illiterate, 37(22.84%) had completed primary level of education, 63(38.89%) had attained a secondary school while 49(30.25%) cases were graduates or post graduates.

In Netherland, Klassen KM *et al* in 2013 observed out of 963cases of nail psoriasis patients, 68.7% cases had plaque psoriasis[22]. Similarly, plaque psoriasis was seen in 74.69% of cases in our study. This mild variation probably could be due to smaller sample size in our study. Nail involvement without any skin changes was seen in 5.55% of cases similar to the observation by Jiaravuthisan MM *et al* in 2007 and de Berker D *et al* in 2009, where both the authors proposed incidence of isolated nail psoriasis to be 5%[3,9].

The Malaysian study conducted by Yap FB et al in 2010 showed 16.4% of psoriatic patients with nail involvement had positive family history[19]. Our study also obtained a resembling result ie, 19.13% patients had similar disease in family members.

Assessing psoriasis area severity index (PASI) in his German study in 2010, Augustin M et al witnessed 15.6% of women and 21.4% of men had PASI score more than 20[18]. Being quite analogous to the above results, 20.91% of people had PASI score above than 20 in our study. But in contrast, Schons KR *et al* in his study in 30 patients with nail changes attributable to psoriasis found 53.3% of them having PASI value less than 10, while it was 20.26% in our study, most possibly due to larger sample size in ours[20].

Taking various co-morbidities in account, in our study 61(37.56%) patients were hypertensive, 37(22.84%) patients had abnormal lipid profile, 33(20.37%) patients suffered from diabetes mellitus, 13 (8.02%) patients had dermatophytic skin infections, 7 (4.32%) patients were diagnosed as having COPD while 4 (2.46%) patients had chronic kidney disease and 3 (1.85%) patients had lichen planus. While these co-morbidities were seen in 60.49% of patients in our study, much the same results were obtained in study of Schons KR *et al* in 2015 where 63.3% patients having nail changes suffered from other co-morbid conditions[20].

Out of 162 patients in our study, diagnosis of nail changes attributable to psoriasis could be only made with a help of a dermatoscope in 29(17.9%) patients while in rest 133(82.09%) patients, the changes were gross and could be easily distinguished by naked eye.

While involvement of both finger and toe nails was observed in 111(68.52%) patients, isolated finger nails and toe nails involvement was visualized in 32(19.75%) and 19(11.72) patients respectively. Schons KR et al also obtained comparable results ie, both finger and toe nail involvement in 70% and isolated finger and toe nail involvement were seen in 20% and 10% of patients respectively[20]. Klassen KM *et al* in 2013 also mentioned 62% cases had both finger and toes involvement while only changes in finger nails and only toe nail changes were seen in 25.3% and 11.2% of cases respectively[21].

Single nail involvement was seen in 22(13.58%) patients while 20 nails changes were seen in 44(27.16%) patients in this study having resemblance to findings of an Indian study by Grover C *et al* in 2005, where the number of nails affected varied from all 20 nails (29%) to a single nail (19%)[22].

Among various components of nail, nail bed was involved in 145(89.51%) cases followed by nail matrix in 121(74.69%) of cases and nail fold in 31(19.13%) patients. Grover C *et al* in 2005 and Kaur I *et al* in 2001 in their studies had found out nail fold involvement in 21.42% and 33.3% of cases, much the same of our study[22,23].

Bedi in his study in 1977 noted nail changes in descending order of frequency, which were pitting, thickening of nail plate, partial onycholysis, subungual hyperkeratosis, yellow-brown discoloration, paronychia, and complete onycholysis[16]. Kaur I *et al* in her study in 2001 in 167 psoriasis patients over a 5years, mentioned pitting to be the most common nail change, followed by onycholysis, discoloration, subungual hyperkeratosis, longitudinal ridging and thickening of the nail plate[23]. Evident nail bed changes observed in study of Grover C *et al* in 2005 were distal onycholysis (76%), subungual hyperkeratosis (33%) and salmon patch (14%) while in study of Klassen KM et al in 2013 changes were onycholysis (57.7%), salmon patch (41.4%), Subungual hyperkeratosis (33.6%) and Splinter haemorrhages (13.5%)[20,21]. While examining nail bed changes in 162 patients in our study both by naked eye and dermatoscope, resembling to above studies onycholysis was seen in 111(68.51%), subungual hyperkeratosis in 48(29.63%), salmon patch in 36(29.63%) and splinter hemorrhage in 59(36.42%) patients.

Prominent clinical nail matrix findings in the observed nails in study of Grover C *et al* in 2005 were discoloration of the nail plate (67%), fine pitting (52%), ragged cuticle with nail fold erythema and scaling (48% each), while in study of Klassen KM *et al* in 2013 obtained results were pitting in 65.4%, leukonychia in 32.1%, red spots in 6.5% of patients[20,21]. Nail matrix changes evident in our study both by naked eye and dermatoscope were pitting 102(62.96%), leukonychia 42(25.92%), red spots in lunula 36(22.22%) and crumbling of nail plate in 73(45.06%) which were quite homologous to the above studies.

When NAPSI as proposed by Rich P *et al* was calculated, 126(77.77%) patients had value in the range of 0-40 followed by 33(20.37%) patients had values from 40 to 80 and 3(1.85%) patients had values within 80 to 120[24].

Natarajan V *et al* in 2010 mentioned about having 47.91% patients with psoriatic nails had onychomycosis[25]. Similarly in our study, 69(42.59%) patients had onychomycosis and 39(24.07%) patients had history of trauma to nails.

In the Malaysian study of Yap FB *et al* in 2010 evidence of psoriatic arthritis was revealed in 20.8% homogenous to our study where this was evident in 20.37%[19]. Augustin M *et al* in 2010 in his German study found 28.7% women and 24.4% men with nail changes had psoriatic arthritis[18]. However in study of Schons KR *et al* in 30 patients, the arthritis involvement had been seen in 43.3% patients[20].

Nail involvement in psoriasis is a marker for more severe cutaneous manifestations and joint involvement. Dermatologists should be familiar with the different clinical presentations of nail changes in psoriasis for an early diagnosis and a more precise determination of patient prognosis. The quantitative assessment of nail psoriasis also allows for a more objective evaluation of the evolution of the disease. Dermatoscope, being a handy, economical, feasible, easily adaptable instrument should hold it place high as a treasured possession in day to day or OPD practices to visualize every subtle nail changes discernible to naked eyes.

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Observational Study

Awareness, outlook & general belief regarding cervical cancer and its prevention in women attending gynaecology OPD in rural setup in West Bengal

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Cervical cancer is a cause of significant disease worldwide. Human papiloma virus (HPV) is the cause of cancer cervix in almost all cases. Early detection and treatment is essential to prevent further spread. It is a well known fact that rural Indian population is usually less informed about cervical cancer and specially screening programmes and available modalities for screening, hence this study was taken to understand their knowledge, attitude & general belief regarding cervical cancer and simultaneously to inform them about the various detection & treatment modalities available. To assess the Awareness & General belief regarding prevention of cervical cancer among women attending gynecology outpatient department (OPD) in rural area setup and to find an association between knowledge and perceived barriers with socio- demographic Variables. The present descriptive study was designed in order to access the knowledge , attitude and belief of rural women based in rural setup of Kalyani. A sample size of 500 women attending Gynaecology OPD in GICE Hospital, aged between 25-55 years was targeted from January 2018 to June 2018. Simple random sampling technique was adapted for the sample collection. Pre tested questionnaire were used for data collection. The rural population in general has a very little knowledge regarding the causes of cervical cancer, signs and symptoms related to it and even have less information regarding prevention methods leading to late diagnosis or even treatment. [*J Indian Med Assoc* 2018; **116:** 39-42]

Key words **: Cervical cancer, Human papiloma virus (HPV), screening of cervical cancer.**

Cervical cancer is one of the dreaded disease of India and worlwide[1]. Most of the involved countries are from low and middle income group. It is a well documented fact that HPV is the cause of cancer cervix in maximum cases[2]. Early age of first intercourse,multiple sexual partners, unprotected sex and sex with un-circumscribed men, have been found to increase the risk of contracting HPV infection[3,4]. It is one of the leading cancer in Indian women and the second most common cancer in women worldwide. Though there are several methods of prevention of cervical cancer, prevention by vaccination is emerging as the most effective option, with the availability of two vaccines[5].

There is very little or no knowledge regarding sources or prevention of the same. The primary reason for this is lack of access to screening and health services, and lack of awareness of the risk factors of the cervical cancer[6].

Perspective of a Cervical Cancer in India :

In India 365.71 million women above the age of 15 are at a risk of developing carcinoma cervix. In 132082 women are diagnosed with carcinoma cervix. In 74118 women die due to ca cervix every year accounting for 26.7% of world wide incidence and 27% deaths worldwide[5].

One women in India dies due to carcinoma cervix every 7 minutes accounting for more than 200 deaths every day. A lot of unexplored area remain regarding cervical cancer, various cervical cancer programmes are running in the country currently. ICMR has national cancer registry which maintain the data. But problem is it does not detect the data from whole country rather than few places of collection points.

The main disparity between low income families and high income families is lack of awareness in former compared to latter and lack of basic health care access to lower/ middle income group.

Methodology :

The present study was designed in order to access the knowledge and attitude of rural women based in rural setup of Kalyani. A sample size of 500 women attending Gynaecology OPD of GICE Hospital, aged between 25-55 years was targeted. Simple random sampling technique was adapted for the sample collection. Pre tested questionnaire were used for data collection. The present study

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was conceptualized and designed in order to assess knowledge and attitude of rural women.

The data analysis was done using SPSS package for analysis, version 16. The outcomes from this study will hopefully point out the major areas that need to be focused in order to build a public campaign to address the cause of cancer cervix, which is one of the leading causes of cancer related deaths in India.

Limitations :

Resource constraints restricted the researchers from taking a truly representative sample of rural women to study their knowledge and attitudes regarding cancer cervix. Also, the researchers feel that ideally there should also have been an action component within the research, at least for IEC activities, which is again limited by the available time and personnel required.

Ethical Concerns :

The study mandated procedures to ensure informed consent and maximize confidentiality. Participation of all respondents in the survey was strictly voluntary and there was no monetary or other compensation offered for participation. Measures were taken to assure the respect, dignity, and freedom of each individual participating in the data collection. Participation was based on informed consent. Each individual agreeing to participate and who was able signed the consent form.

Findings

This survey asked respondents via multiple choice questionnaires,questions about the cervix, cervical cancer, screening test, pap smear test, willingness to pay, perception regarding pap smear testing, HPV vaccination, willingness to pay for vaccination. Questions were spread out to assess knowledge and attitude regarding both screening and vaccination.

Respondent Profiles :

In 49% of the respondents were in the age group of fifteen to twenty five years. This primarily includes school and college going students. In terms of educational qualification of the respondents, more than 20% of the respondents have received at least graduate degree. 40% had annual income less than Rs 50000 (Table 1)

Table 1 — *Annual Family Income of the Respondents*

< 50000	40 %
50000- 1lakh	20 %
1 lakh – 2 lakhs	20%
>2 lakhs	20%

Only 5% of respondents (Table 2) could identify the correct symptoms that a patient with cervical cancer may show and 80% said that they do not know what could be the symptoms of cervical cancer. Of this latter group which said they do not know the symptoms, the highest number were of housewives and school students. Only 15% could identify the possible effects on cervical cancer on a patient, of this maximum women were employed and were "employed" group of the respondents. When asked about the age group most likely to get cervical cancer, only 24% said that it is menopausal age group. 49% had no idea (Table 3)

Table 2 — *Knowledge of symptoms*

Correct symptoms	5%
Do not know symptoms	80%
Possible symptoms	15%

Table 3 — *Age group likely to get cervical cancer*

Reproductive group	12%
Menopausal group	24%
Any age group	15%
Don't Know	49%

Question	Respondents %
Know screening	15
Know pap test	12
Had pap test	30
Pap test is safe	14
Pap test in every two years for adult	29

Knowledge and Attitude Towards Screening Test :

This section of the study started by asking the respondents if they know what is a screening test. Equal responses were received for choosing the correct definition from the given options and for opting for "don't know". However, in response to the next question, 12% of the respondents said that they have heard about a pap smear test. Of these 12%, the highest proportion was of employed women.

Consequently, this was also the category that had the maximum number of affirmative responses for ever having taken a pap test. Interestingly, in 3 % of the cases the pap test was self prescribed. The amount paid for the test ranged between 100 to Rupees 200.

When asked how much is a respondent willing to pay for screening test most of them say that it should be within Rs.500. Around 50% respondents of this hold some kind of health insurance. Only 14% respondents perceive PAP test to be safe, as against being risky and painful. On being asked if a healthy adult women should have a pap test every two years, maximum responses are registered as "cannot say". While 33% of respondents agree, 29% disagree (Table 4).

Table 4 — *How much you are willing to spend on Pap Test every two years*

Free	40%
Rs 50	11%
Rs 50-100	5%
Rs 100-200	3%
Rs 200-500	32%
Rs 500-1000	09%

Knowledge and Attitude Towards Colposcopy as a Diagnostic Tool :

While from above it's noted that knowledge about PAP Smear is highly limited among rural population, the subjects are even unaware about colposcopy. 88% has no idea regarding colposcopy, surprisingly even after explaining the uses 80% doesn't consent for usage considering the fact that national cancer research institute are advocating use of colposcopy in field setup (Table 5)

Knowledge and Attitude Towards HPV Vaccination :

In 80% do not know anything about the HPV vaccine. 61% can't say if HPV vaccine can prevent them from cervical cancer. 35% (Table 6 & 7) would like to take HPV vaccine as a preventive measure against cervical cancer. Most of the respondents 28% are willing to spend within Rs. 1000 to get the vaccination. 92% of respondents do not know where HPV vaccine is available, while 13% say that it is able in private clinics, Government health facilities and in medical stores.

Table 5 — *Idea about Colposcopy ?*

Yes	12%
No	88%
Will consent to use	20%
Will not consent to use	80%

Table 6 — *Would like to take HPV vaccination as a prevention against cervical cancer*

Yes	35%
No	40%
Can't say	25%

Table 7 — *HPV Vaccine can prevent you from cervical cancer*

Agree	27
Disagree	12
Can't say	61%

Decision Making Environment :

On being asked who decides in the family when to see a doctor, 44% said that the decision making is done according to the situation in hand and 35% said that they themselves decide when to seek medical care. It was also asked if they would be comfortable in talking about cancer screening to their guardians (or at home), to which 50% respondents answered in affirmative. However, 16% said they would do so only if it was urgent and 30% said they don't know (Table 8).

Table 8 — *Will you be comfortable in talking about cancer screening to your guardians*

Yes	50%
No	4%
Only if its urgent	16%
Don't know	30%

Discussion

There is a lack of awareness regarding cervical cancer and HPV Vaccination, the general population at large is ignorant of the disease and prevention. But is willing to know and spend some amount for better screening. They also have positive perceptions about the HPV vaccination to prevent cervical cancer among the studied group. Beliefs and practices of preventive health seeking behavior primarily assessed through the respondents knowledge and perception regarding cancer screening (pap testing) are not based on any concrete evidence or information. The cause for above statement may be due to lack of awareness programmes, education or communication to community at large. The community elders also play almost negligible role in spreading information during major gatherings.

Knowledge about linkage between HPV and cervical cancer and hence HPV vaccine and cervical cancer is also absent in half of the responses. The peak incidence of HPV occurs between the ages 16 and 20 yrs, after the first sexual intercourse. The natural history of HPV infection coupled with the ability to clinically access the cervix makes cervical cancer the most preventable and treatable of all types of cancer. The dual application of primary and secondary prevention strategies offers an opportunity for comprehensive control of this cancer[7].

There is higher incidence of ca cervix in developing countries than the developed countries. In low income countries,middle aged women have at least as many as HPV infections as young women, mainly because of variations in the age specific sexual behavior of the women and their partners[8]. Socioeconomic differences in cervical cancer risk seem to be explained not by differences in HPV prevalence but rather by factors that affect the natural history of HPV infection (eg, Early age at first sexual intercourse and child bearing, and high parity). Immune impairment due to HIV infection also leads to many fold increases both in the burden of HPV infection and in the already existing lack of adequate screening for cervical cancer.

This rural study can be a eye opener to even do larger studies and to involve more rural population at large. This is just a questionnaire based study to elicit information from rural population. There is a need for large scale screening programmes.

Another important dimension is availability of HPV Vaccine in government supply chain, as of now it's not available and cost can be a deterrent factor for rural household.

In this study, many women suggested they can afford maximum of Rs 500 for it. In this regard, several models of economic evaluation indicate that HPV vaccination in low and middle income countries where quality screening is not wide effective if the cost per vaccinated girl(including 3 doses of vaccine and program costs) is less than US$ 10-25[8].

What is required is commitment from government, and to follow three models, of HPV Vaccination, screening and treatment, More research is required regarding use of HPV Vaccinations and its viability in terms of cost among general population including government supply of vaccinations.

Conclusion

Every public health programme requires dedication from grass root level, it can be taken as a challenge to provide adequate healthcare to poor by government but implementation in this vast country is difficult. Hence po-

litical is also very important in this regard. Screening program for cervical cancer is nowhere on the national public health policy priorities. The Government of India has already launched a National Cancer control programme in 1975.

With a prime focus on early detection and primary prevention but implementation is hard to see yet.

Hence focus should be concentrated on following points:-

(A) Health education.

(B) Behavior change communication regarding preventive care seeking.

(C) Setting up primary prevention facilities.

(D) Plan and strategize for and extensive screening program and

(E) Deliberate on the possibility of introduction of the HPV vaccination

This study regarding awareness has opened our eyes regarding lack of knowledge in rural areas about cervical cancer and the need to open our eyes and to persuade the government to consider cervical cancer screening as one of the top priorities in country.

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Observational Study

Retrospective study of feto-maternal outcome in Hepatitis E infection in third trimester of pregnancy at a tertiary care hospital in Western India

Rajal V Thaker[1], Parul T Shah[2]

To study of Feto-Maternal outcome in Hepatitis E (HEV) infection in third trimester of pregnancy and to suggest measures for its prevention during pregnancy. After due permission, course of disease and feto-maternal outcome was studied from case papers of patients who were infected with Hepatitis E during third trimester of pregnancy. Analysis of data of 38 patients was done. Proportion of Hepatitis E in third trimester of pregnancy was 0.19%. Maximum numbers of patients 6(15.7%) were reported in months of September and November each. Maximum numbers of patients 23(60.5%) were in age group of 20 to 25 years. Majority 33(86.8%) patients were from lower socioeconomic class. Majority 32(84.2%) patients were emergency admissions. Serum bilirubin was more than 5mg/dl in 35(92.1%). Alkaline phosphatase and serum transaminases were raised in 30(79%) and 33(86.9%) respectively. Coagulation tests were altered in 24(63.1%) patients. Preterm normal deliveries were 21(67.7%) and 6(19.3%) were preterm Caesarean Section (CS). Low birth weight (LBW) was reported in 27(87%). Stillbirths were 7 (22.5%). Perinatal mortality was 11(35.4%). Out of all, 25(65.7%) patients had complications. Disseminated Intravascular Coagulation (DIC) was the most common complication encountered in 24(63.1%). Hepatic encephalopathy occurred in 11(28.9%). Blood components were given in 29(76.3%) of patients. Total 8(21%) patients died following fulminant hepatic failure (FHF), Disseminated Intravascular Coagulation (DIC) and Hepatic encephalopathy. Equal number of patients died in antenatal and postnatal period that, is 4 (10.5%) in each period. Hepatitis E infection in third trimester of pregnancy has a worsening course leading to high feto-maternal morbidity and mortality; hence prevention of Hepatitis E infection in pregnancy is very essential.

[*J Indian Med Assoc* 2018; **116:** 43-6]

Key words **: Hepatitis E in pregnancy, Jaundice in pregnancy, HEV and pregnancy.**

Pregnancy with jaundice is considered as a high risk pregnancy. Viral hepatitis is the most common cause of jaundice in pregnant women. Seven types of virus can cause viral hepatitis; called hepatitis A to G. Incidence of hepatitis varies greatly around the world. In 89,80,000 cases of viral hepatitis with 5,85,800 deaths occur annually in South East Asia. In addition to the loss of more than 0.5 million lives and untold suffering for millions of people, viral hepatitis causes tremendous economic loss to the patients, and their families due to long hospitalization and expensive treatment for chronic patients[1].

Hepatitis E is a single stranded RNA virus (HEV) that leads to an estimated 20 million hepatitis E infections, over three million acute cases of hepatitis E, and 57 000 hepatitis E-related deaths[2]. Four studies from Delhi, India have reported a prevalence of HEV infection in pregnancy as 18%, 37%,47.4% and 60%[3-6] respectively. This infection often occurs in water born epidemics, spread by faecooral route and is clinically similar to hepatitis A. The resultant liver disease is usually mild, except in pregnant women, particularly those in the third trimester[7] where it can be aggressive and patient may develop fulminant hepatic failure (FHF) with high feto-maternal mortality and morbidity.

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Material and Methods

This retrospective observational study was conducted after due permission from authorities. Course of disease and feto-maternal outcome were studied from case papers of patients who were infected with Hepatitis E (positive with IgM HEV antibodies detected by Enzyme Linked Immuno Assay - ELISA) during third trimester of pregnancy admitted at a tertiary care hospital, Sheth V S General Hospital affiliated with Smt NHL Municipal Medical College at Ahmedabad, Gujarat in western India during July 2008 to June 2012. Data was collected as per pretested structured proforma. Analysis of 38 patients was done regarding age, parity, residential status, education,

timing and whether registered or emergency admissions. Data regarding pregnancy outcome, Obstetric complications, transfusion of blood and blood products, maternal and perinatal mortality were analyzed.

Results

It was observed that, overall management of HEV during pregnancy is not different from managing jaundice due to other causes of viral hepatitis. All patients were referred to general physician and gastroenterologist. If required, patients were transferred to Medical Intensive Care Unit (MICU). Repeat investigations were carried out as and when required. Those patients who showed worsening of disease were induced and delivered vaginally. Caesarean section was performed if required. Help of neonatologist was also taken and whenever required, babies were admitted at Neonatal Intensive Care Unit (NICU). Patients showing improvements of signs and symptoms and improved laboratory investigations were managed conservatively.

Analysis of data of 38 patients was done. From July 2008 to June 2012, 19,977 deliveries had taken place. Hence, proportion of Hepatitis E at our institute was 0.19%. Maximum numbers of patients 6(15.7%) were reported in months of September and November each, followed by 5(13.5%) in June. In months of May, July, August, October and December, 3(7.8%) patients were reported in each month. Maximum numbers of patients 23(60.5%) were in age group of 20 to 25 years. There were 34(87.1%) patients who belonged to the age group 20-30 years. Patients from urban areas were 29(76.3%). Majority 32(84.2%) patients had at least primary education. Majority 33(86.8%) patients were from lower socioeconomic class. Majority 32(84.2%) patients were emergency admissions. Out of them, 20(52.7%) were Primi, 11(28.9%) were second gravida and 7(18.4%) were multigravida. Most common presenting symptom was abdominal pain in 33(86.8%) patients. This was followed yellowish discoloration of urine in 29(76.3%), by loss of appetite, nausea and vomiting in 28(73.7%), fever in 12(31.5%), itching in 8(21%), irritability and altered sensorium in 6(15.7 %). More than one symptom was present in each patient. Icterus was present in all patients. Yellow discoloration of skin and fever were present in 22(57.9%) and 12(31.5%) respectively. Matenal Hepatomegaly was present in 9(23.7%), ascites was present in 7(18.4%) and splenomegaly was present in 5(13.1%). Majority 26(68.42%) patients were anaemic. TLC was raised in 20(52.6%) and 8(21%) had thrombocytopenia. Serum bilirubin was more than 5mg/dl in 35(92.1%) and 8(21%) had more than 15mg/dl. Alkaline phosphatase and serum transaminases were raised in 30(79%) and 33(86.9%) respectively. Tests of coagulation were altered in 24(63.1%) patients. As shown in Table 1, Preterm normal deliveries were 21(67.7%) and 6(19.3%) were preterm Caesarean Section (CS). Full term normal delivery, forceps and CS were 2(6.5%), 1(3.2%) and 1(3.2%) respectively. Indications of CS were fetal distress in 3, non progress of labor in previous CS in 3, and previous 2 CS in one patient. During antenatal period, 4(10.5%) patients expired undelivered and 3(7.8%) had come in early third trimester who were discharged after complete recovery, that means patients were discharged after they became asymptomatic and after their laboratory indices became normal but then they had not come for follow-up and for delivery at our institute; hence they were lost for follow up of their feto-maternal outcome. Table 2 shows, Outcome of baby. Liquor was meconium stained in 16(51.6%). Low birth weight was reported in 27(87%). Stillbirths were 7(22.5%). NICU admissions were 11(35.4%), out of them 4(12.9%) died. Perinatal mortality was 11(35.4%). Out of all, 13(34.2%) patients had no complications, whereas 25(65.7%) patients had complications as shown in Table 3. More than one complication was found in some patients. Disseminated Intravascular Coagulation (DIC) was the most common complication encountered in 24(63.1%). Hepatic encephalopathy occurred in 11(28.9%). Wound complications like hematoma and infection of CS wound occurred in 4(10.5%) patients. Other significant complications were PPH and renal failure occurred in 2(5.2%) each.

Table 1 — *Outcome of Pregnancy*

Outcome of Pregnancy			Number	Percentage (%)
Delivered N = 31 (81.5%)	Preterm 27(87%)	ND	21	67.7
		CS	06	19.3
	Full term 4(12.9%)	ND	02	6.5
		Forceps	01	3.2
		CS	01	3.2
Undelivered N=07 (18.5%)		Expired	04	10.5
		Discharged and lost for follow up	03	7.9

Table 2 — *Outcome of Baby*

Outcome of Baby N = 31 (81.5%)		Number	Percentage (%)
Live Birth		24	77.4
Still Birth		7	22.5
Weight	< 2 kg	15	48.3
	2.1-2.5 kg	12	38.7
	> 2.5 kg	04	12.9
NICU admission		11	35.4
Died within 7 days		04	12.9

Table 3 — *Maternal Morbidity*

Maternal Morbidity N = 25 (65.7%)	Number	Percentage (%)
Disseminated Intravascular Coagulation	24	63.1
Fulminant Hepatic Failue, Hepatic Encephalopathy	11	28.9
Wound complication	4	10.5
Post Partum Hemorrhage	2	5.2
Renal Failure	2	5.2

Blood components were given in 29(76.3%) of patients. Packed Cell Volume (PCV), Fresh Frozen Plasma (FFP), Platelet Rich Concentrate (PRC), and cryoprecipitate were given in 12(31.5%), 27(71%), 8(21%) and 5(13.1%) of the patients respectively. As shown in Table 4, total 8(21%) patients died following FHF, DIC, Hepatic encephalopathy and Septicemia. Majority of maternal deaths 6(15.7%) occurred due to FHF and Hepatic encephalopathy. Equal number of patients died in antenatal and postnatal period that, is 4 (10.5%) in each period. There were 6(75%) maternal deaths amongst emergency admissions.

Table 4 — *Maternal Mortality*

Maternal Mortality (N = 8)	Number	Percentage
Fulminant Hepatic Failure, Hepatic encephalopathy	6	15.7
PPH, DIC, Renal Failure	1	2.6
Septicemia	1	2.6
Total	8	21

Discussion

In our study, HEV infection was found almost any time in a year, but more so in months of summer and monsoon season. In our study, 34(87.1%) were below 30 years. In a study by Caro *et al*[8] more than 2/3 of patients were below 30 years. Early marriages along with unclean, unhealthy and improperly cooked food among these pregnant women may be a cause of the infection. In our study, majority of patients were from lower socioeconomic status. Kumar *et al*[9] has also reported similar findings. In our study, more than half of patients were primigravida. In a study by Malahat M *et al*[10] 36.3% were primigravida.

In our study, 13(34.2%) patients had no complications and were managed conservatively as there was improvement in clinical and lab indices. In our study, induction of labour or caesarean section was done as and when required.

Therapeutic termination of pregnancy, which has been proved to be beneficial in pregnancy specific disorders like HELLP(Hemolysis, Elevated Liver enzyme, Low Platelet) syndrome and acute fatty liver of pregnancy[11] have not been fully, explored in Hepatitis E infection. However in a retrospective study from India[12] in 42 patients with HEV induced liver failure, there was no difference in maternal mortality in pregnant women who delivered and those who did not questioning the role of therapeutic termination. At present, although there is no consensus to treat patients with HEV infection in pregnancy, early delivery of the fetus if possible to prevent maternal mortality should be tried. Randomized studies are required in the future to decide upon the best way of treating patients with HEV infection in pregnancy[13]. It has been observed that among pregnant patients, the decision to continue pregnancy with increasing levels of bilirubin and other liver functions tests, the mortality rate is high[14]. Hence conservative management or "wait see" policy should only be followed if the patients show signs of clinical and laboratory indices improvement[15]. At our hospital, we also follow the conservative management approach if patient show improvement in clinical and laboratory indices.

In our study, there were 23 (74.1%) vaginal delivery and 8 (25.8%) operative delivery. Generally, cesarean section has higher morbidity compared to vaginal delivery. Hence, vaginal delivery is always preferred in these patients to prevent complications due to cesarean section and in presence of complications like hepatic encephalopathy and hepatic failure. In our study, we found that, stress of labour has no role in deterioration of disease.

Our study revealed that, the liquor was meconium stained in 16(51.6%) and 7(22.5%) were stillbirths. Malahat M *et al*[10] has reported 15% rate of stillbirth with HEV infection. This may indicate the chance of vertical transmission which may cause fetal death.

Our study revealed that there was a high percentage of preterm labour and low birth weight in 27(87%). Kumar *et al*[9] observed that prematurity in HEV affected fetuses was 84%. Suruchi S *et al*[3] has reported 6% of intrauterine death and 41.3% of low birth weight baby in mother having HEV infection. In our study, 11(35.4%) babies were admitted in NICU and out of them 4(12.9%) died. Perinatal mortality was 11(35.4%). With better NICU facility at our hospital neonatal mortality and morbidity is low compared to other studies[10,16] where it was 47% and 54% respectively.

Our study revealed that, 25(65.7%) patients developed complications. More than one complication was present in some patients. DIC was the most common complication encountered in 24(63.1%). Hepatic encephalopathy occurred in 11(28.9%) and ventilator support was required. Wound complications like hematoma and infection of CS wound occurred in 4(10.5%) patients. Other significant complications were Post Partum Haemorrhage (PPH) and Renal failure seen in 2(5.2%) each. Blood components were given in 29(76.3%) patients. Some patients were given more than one component. Transfusion with PCV, FFP, Cryoprecipitates and Platelets are usually necessary for management of severe anaemia, PPH and Coagulation defects. Patients who developed renal failure were managed with dialysis. Patients who developed FHF were managed at MICU with supportive care. They received 25% Dextrose, Vitamin K, lactulose, antibiotics, refaximine, parenteral intervention if required and ventilator support if and when needed. Thus, Multidisciplinary approach by Gastroenterologist, Nephrologist and availability of blood components at our tertiary care hospital have played a crucial role in management of complications. Several cross-sectional studies where feto-maternal outcome in pregnancy due to Hepatitis A, B, C and E viruses were compared, it was seen that incidence of FHF was highest in patients suffering from Hepatitis E[3]. Beniwal M *et al*[5] has reported that, HEV was responsible for 75% cases of FHF and maternal mortality was 39.1%. The cause

of the increased severity of this hepatitis during pregnancy is unknown, but may relate to attenuated cellular immunity during pregnancy.

In our study, equal number of patients that is 4 (10.5%) each, died in antenatal and postnatal period. Out of these, 6(75%) maternal deaths were reported in emergency admissions that were brought in very late stage with altered sensorium. These patients could have been saved if they were brought early. Although, proportion of Hepatitis E was 0.19% during the study period, maternal mortality was 8(21%) following FHF, DIC, Hepatic encephalopathy and septicemia. Of those who died in post natal period, one patient also had Renal Failure following DIC and PPH and other also had Septicemia. According to WHO[2], pregnant women are at greater risk of obstetrical complications and mortality from hepatitis E, which can induce a mortality rate of 20% among pregnant women in their third trimester.

In our study, higher levels of Serum bilirubin, Alkaline phosphatase and serum transaminases were associated with higher maternal mortality. No Maternal mortality reported when initial serum bilirubin was less than 5 mg%. Prolonged hospital stay contributes to more financial burden either on family or on Government. Feto-maternal mortality is in addition a great loss to family and to society.

Prevention of Hepatitis is very important especially in developing countries. Public health education helps in creating awareness regarding different modes of transmission of hepatitis. Pregnant women are best advised to avoid contact with suspected HEV cases and it can be minimized by adapting hygienic habits like hand washing with safe water. Better sanitation facilities, safe drinking water, avoiding uncooked food and disposing of contaminated clothes and fomites by autoclaving and incineration also helps. Increased availability of antenatal care for early detection and aggressive management of pregnancy with jaundice at tertiary care center with multidisciplinary approach will help in the reduction of maternal and perinatal morbidity and mortality.

Conclusion

Hepatitis E in third trimester has a worsening course in pregnancy that affects both fetus and mother. There is high risk of preterm delivery, fetal distress, IUD and meconium aspiration leading to high perinatal mortality and morbidity. HEV also has grave prognosis with high maternal mortality. Conservative management should only be followed if the patients show improvement in clinical signs and laboratory indices. Obstetric management along with NICU facility and multi disciplinary approach at a tertiary care center can help in reduction of maternal and perinatal morbidity and mortality. Prevention of HEV is also necessary. Hence, all antenatal women along with their family members should be made aware regarding different modes of transmission of hepatitis during their antenatal visits.

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Case Report

Squamous cell carcinoma in mature cystic teratoma of ovary

Manjula Manchale K[1], Praveen B. Biradar[2]

A 45 year-old female presented with distention of abdomen since 6-8 months. Ultrasonography revealed a cystic mass with solid areas arising from ovary and was diagnosed as a dermoid cyst. Total abdominal hysterectomy with bilateral salphingo-ophorectomy was performed. Cut section of left cystic ovarian mass showed tuft of hairs seen as a ball and yellow pultaceous material. Also seen were solid grey-white areas. Histopathological study confirmed the findings of dermoid cyst and grey-white solid areas showed squamous cell carcinoma with areas of keratin material, lymphocytes and mitotic figures. The right ovary was normal. Post-operative period was uneventful.

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Key words **: Squamous cell carcinoma, dermoid cyst, ovary.**

Dermoid cyst consists of tissues that develop from ectoderm, endoderm and mesoderm. Teratomas in majority of cases are benign in character and with complete surgical excision offer a very good prognosis[1]. Malignant transformations are rare, occurring in 2% of cases[2]. Squamous cell carcinoma is more common than adenocarcinoma and primary squamous cell carcinoma is a rarity[3].

Case Report

A 45 year-old female presented with distension of abdomen of 6-8 months duration. She had two children with normal obstetric history. No history of loss of weight, appetite or any bowel and bladder symptoms. Clinical examination revealed a palpable mass in the left iliac fossa arising from pelvic cavity of 16th week size. Ultrasonography showed a left-sided ovarian mass with cystic and solid areas. Liver and spleen were normal. Total abdominal hysterectomy with bilateral salphingo-ophorectomy was done showing large left-sided cystic ovarian mass. removed. Uterus, cervix and right ovary appeared normal.

Gross Examination — The cystic ovarian mass measured 16x12x9cms with outer surface showing solid areas measuring 5.5x4.5cms. Cut surface exuded grey-yellow pultaceous material and showed tuft of hairs in a ball like appearance. Cut surface of solid lesion showed a tiny cystic area measuring 2x1cm and appeared grey-white.

Histopathological Examination — Sections showed a cyst wall lined by stratified squamous epithelium with adnexal structures. The solid areas showed atypical squamous cells, with keratin deposits, inflammation and mitotic figures. As there were no evidence of squamous cell lesion anywhere in the patient, the final diagnosis of mature cystic teratoma with squamous cell carcinoma was made.

Discussion

Mature cystic teratoma of ovary comprises about 25% of all ovarian tumors[4]. They usually contain putty-like material and various organised mature tissues. Malignant transformation can occur from any germ layer[2]. Much more often the malignant lesion, derived from one of the elements of an otherwise benign teratoma is a carcinoma and in the series of cases studied by Peterson (1956) the commonest carcinoma was of squamous cell type of all instances[5]. Matz MH(1961) reported 85% of mature cystic teratoma in the age group of 16-55 years, mean age being 35 years[6]. Kikawa *et al* in his study of 37 cases of squamous cell carcinomas arising from mature cystic teraoma of ovary observed that mean age of squamous cell carcinoma was 55.2 years as compared to 37.5 years in patients with benign cystic teratoma. The mean size of malignant dermoid tumor in his study was 152.3 mm compared to 88.4 mm in benign dermoids. Women older than 45 years and tumor size greater than 99 mm were the criteria for malignancy[7]. Pure squamous cell carcinoma arising from metaplasia of surface epithelium of ovary and malignant transformation of ovarian endometriosis is still rare[8]. Metastasis from cervical squamous cell carcinoma is again an uncommon occurrence, the incidence being 0.5%[9]. An interesting occurrence of synchronous cervical, endometrial, tubal and ovarian squamous cell carcinoma and cervical intra epithelial neoplasia due to HPV infection has also been reported[10].

Conclusion

Primary squamous cell carcinoma of ovary is rare. Metastasis of squamous cell carcinoma to the ovary is still rare. The malignant transformation being common from the 4th decade of life. The case presented here is a pure malignant transformation in a mature cystic teratoma and due to its rarity has been reviewed in the literature.

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Case Report

Paraplegia following Subarachmoid Block

R Varaprasad[1], K Priyathama Sankar[2]

Paraplegia, a serious complication following spinal anaesthesia is associated with significant morbidity and even mortality.Incidence of neurological complications following neuraxial block is between 1/1000 and 1/1,000,000. Neurological disturbances following spinal anaesthesia are less frequent. Most of the observed ones have been transient or have left minimal neural deficits. Rarely extensive and permanent damage to the nervous system may occur. Many problems concerning the pathogenesis of the neural complications of spinal anaesthesia remain unresolved. We are reporting a rare case of paraplegia following spinal anaesthesia given for total abdominal hysterectomy in an ASA physical status II patient. The delay in recovery of sensory and motor loss below T_{10}(paraplegia) may be attributed to the triggering of acute myelitis due to spinal anaesthesia.

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Key words **: Paraplegia, transverse myelitis, spinal anaesthesia, bupivacaine.**

Case Report

A 36 year old female, weighing 68 kilograms, presented with uterine fibroid, polycystic ovarian disease and chronic cervicitis, was posted for total abdominal hysterectomy. She has history of diabetes mellitus for eleven years and hypothyroidism for nine years. She was taking regular medication for both the diseases. Her fasting and postprandial blood sugars and thyroid profile were normal. Her fasting blood sugar on the day of operation was 85mg/dl. Her haemogram, serum electrolytes, renal function tests, electrocardiogram, echocardiography, chest X ray were normal. Vital parameters were normal.

Under strict aseptic precautions, spinal anaesthesia was given with 25 gauge Quincke's needle and 0.5% heavy bupivacaine 3ml (15mg) was given at lumbar 3rd-4th interspace. Sensory loss was up to the level of T_8 with adequate relaxation. Sensory loss was judged by pinprick and motor loss by Bromage scale. Surgery which lasted for forty five minutes was uneventful. Intraoperative parameters were within normal limits. Postoperative vitals were stable with a MAP of 90+/-10. One litre of Ringer lactate was transfused during surgery. The sensory and motor loss continued after the completion of surgery and was considered an abnormal delay in recovery.

Sensory loss below umbilicus and motor loss of both lower limbs persisted even on the first postoperative day. Motor power of lower limbs was 0/5, tone: hypotonic, reflexes absent, plantar reflex absent.

Sensory level: Loss of sensation below T10 level

Bilateral dorsalispedis pulsations were present.

Bowel and bladder reflexes were lost.

Neurophysician was consulted. MRI revealed acute myelitis. No epidural haematoma was found.Conusmedullatis was mildly bulky with rounded contour.

Treatment was started with injection methylprednisolone 1gm intravenous in 100ml normal saline slowly over 20 minutes for 3 days followed by prednisolone 60mg orally along with physiotherapy.

On second postoperative day patient complained of heaviness and numbness of both upper limbs which subsided on third postoperative day with the present treatment.

A possibility of post spinal acute myelitis was considered. The status of the patient remained static and showed no improvement for nearly one month. After one month of treatment patient was complaining of weakness, numbness of both upper limbs, more on the left half of the body with visual disturbances floaters; fundoscopy was normal.

MRI repeated after one month showed no significant changes in the brain.

MRI spine revealed swelling and thickening of spinal cord extending from C_2 to conusmedullaris (whole cord involvement)

Taking into consideration, a relapse of illness and progression of the lesion, a possibility of demyelinating illness, neuromyelitisoptica was considered, Aggressive treatment was restarted with high doses of injection methylprednisolone followed by tapering doses of oral prednisolone. After immunoglobulin test, IgG 30 g was given for three days.

MRI repeated after three months showed atrophy of brain.

Subsequently, after a total period of six months the patient expired.

Discussion

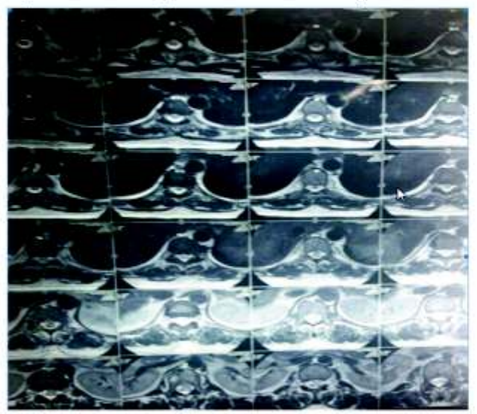
Paraplegia, a serious complication following spinal anaesthesia is associated with significant morbidity and even mortality. Complications following regional anaesthesia have been recognised since a long time. Bier reported hundred years ago[1]. Although rare, neurological complications due to spinal anaesthesia are more than those of epidural. The studies being retrospective, the possible causes attributed are infection, febrile, immuno-compromised, pre-existing neurological disorders and those on anticoagulants[2]. Variations in the oxidative stress and antioxidant levels lead to auto immune disease. Thyroid hormone level is associated with the oxidative and antioxidant status. A study found that Acute Transeversemyelitis patients had lower levels of TSH and FT3 and higher levels of FT4; the severity being inversely proportional to the levels of TSH and FT3[3]. Pathological studies have shown a relationship between diabetes mellitus and myelopathy, the posterior column lesion more common than the cortico-spinal tract. The combination of peripheral neuropathy, disturbed sense of position and/or vibration and pyramidal signs are suggestive of diabetic myelopathy. Although myelopathy is rare, it is one of the debilitating neurological complications of diabetes mellitus[4]. Pre-existing neurological injuries caused by abnormal medullary circulation like diabetes mellitus, atherosclerosis and cervical injury can lead to infarction of anterior 2/3 of the spinal cord causing flaccid paralysis of the lower limbs[5]. Paraplegia following spinal analgesia has been reported in case of congenital absence of lumbar vertebra[6]. Rare causes are GB syndrome, epidural abscess attributed to bacteraemia or neighbouring infectious process (1:50,000 patients) can coincide with the procedure[7]. Epidural haematoma can occur in obstetric patients with abnormal coagulation or low platelets, chronic renal failure hepatic cirrhosis and liver failure[8].

Our prime concern was to exclude spinal anaesthesia as a cause for paraplegia- we needed to exclude spinal cord haematoma, spinal cord abscess, caudaequina syndrome, arachnoiditis, transverse myelitis, anterior spinal artery syndrome, disc prolapse, vertebral tuberculosis or vertebral metastasis. Urgent MRI of the brain and spinal card was done to come to a diagnosis. The changes are mild abnormal altered T2W hyperintensities noted in dorsolumbar from D2 to L1 level with mild expansion of the cord and heterogeneous T2W and signal changes confirmed of acute trandeversemyelitis.

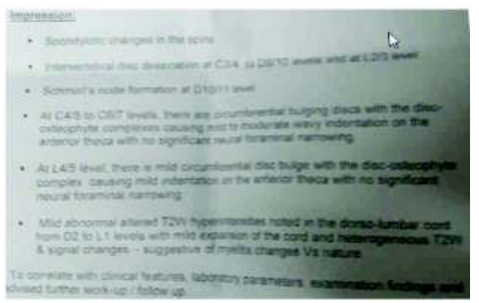
Philip K Bromage has classified neurological complications into three classes- those from non-anaesthetic causes,, or underlying pathology aggravated by regional analgesia and those related to regional analgesia[9]. In a metanalysis of 65,206 patients, five had neurological sequelae - epidural block with 2% procaine, 1% lignocaine with or without 1:20000, 000 adrenaline, mepivacaineand chlorprocaine[10]. The deficits ranged from flaccid paralysis to cellular degeneration of the anterior two third of the spinal cord[9]. Delayed recovery from epidural labour analgesia occurred in two cases with 2% chlorprocaine. One patient recovered in 72 hours and the other made partial recovery in four weeks[11,12]. Complete flaccid paralysis was reported by Sameer etal in an eighteen year old patient without any underlying cause as all preoperative investigations were normal. So, a probable diagnosis of aseptic or viral meningitis was made[13].

Our patient had no pre-existing neurological disorder; she was suffering from diabetes mellitus for eleven years and hypothyroidism for nine years but under control. Rest of the preoperative investigations were normal. Strict aseptic precautions were taken during spinal puncture and the same batch of local anaesthetic was used for many other patients. Immediate postoperative MRI was transverse myelitis which was triggered by spinal anaesthesia was the probable cause of the paraplegia, subsequently quadriplegia and respiratory muscle paralysis leading to her death.

MRI of total spine



MRI of dorsal spine



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Conclusion

Long standing hypothyroidism can lead to autoimmune disorder in the form of acute transeverse myelitis. The associated diabetes mellitus can be an aggravating factor to the disease. Any intervention such as neuroaxial blocks or nerve blocks can precipitate neurological complications. General anaesthesia would be a better option.

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Special Supplement on NEPHROLOGY

Editorial

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Anticoagulant free hemodialysis

Anticoagulant is necessary to prevent blood clotting in the dialysate. Unfractionated heparin is the anti coagulant of choice. However, in many clinical situations, anticoagulant is strongly contraindicated, like recent surgery, intracranial bleeding, GI bleeding, poly trauma etc. When blood flow kept low as in continuous renal replacement therapy or sustained low efficiency dialysis, possibility of clotting is high and some form of anticoagulation is necessary. Regional citrate is suitable in these situations. However, citrate anticoagulant is not freely in India. Normal saline flush 100ml every 10 to 15 min. interval into the blood compartment prior to filter flushes dialyzer and venous chamber as well is commonly used. In some blood tunings there is a net filter in the venous chamber and clotting starts there. If no clotting detected the procedure repeated every 10 to 15 min interval. When the blood flow is low as in prolonged intermittent therapy, clotting still happens esp. when flushing is delayed. 5-10% filter clotting is reported with this technique.

In the current study, pre delusional hemodiafiltration used as means of coagulant free dialysis. Typically it provides sterile dialysate fluid infused 10 to 25 liters continuously into the blood compartment, diluting blood and prevents clotting. When blood flow is good and more than 250 ml/min, substitution volume is also close to 20liters/4hr. HDF session, and there is little clotting. On the other hand, when blood flow is low as 100ml/min, the infusate volume is typically 10 liters/4-6hr HDF session, there is increased chance of clotting and need additional flushing of the dialyzer. The substitution volume is typically linked to blood flow keeping in mind the post filter delusional method. Higher the blood flow, more substitution fluid. The ultrafiltration rate kept maximum up to 20% of the blood flow to prevent blood clotting. Only in some models, the substitution volume may be fixed manually in pre-delusion method.

The additional cost of the procedure is negligible. It consumes more dialysis concentrate, and cost may be less than 100 rupees per session. The major advantage with this method is it provides hemodiafiltration as opposed to hemodialysis. This gives a better middle molecular clearance and much more hemodynamic tolerance.

If the intermittent therapy is prolonged up to 6-8hrs. and blood flow kept less than 250ml/min. additional flush every 20-30min. interval is necessary. When the session is 4hrs. and blood flow is more than 250ml/min. additional infusion is not necessary. For a check, one flush at the end of 15min. period from the beginning, and absence of clotting will be reassuring. We find this method is very helpful.

Original Article

Post-transplant human cytomegalovirus infection can lead to deterioration and dysfunction of renal allograft tissue

Arpita Ghosh Mitra[1], Nasifa Hasan[2], Soma Choudhury[2], Saheli Podder[2], Ankita Das[2], Sudip Roy[3], Nikhilesh Raychaudhuri[4], Dilip Kumar Pahari[5]

Human Cytomegalovirus (HCMV) infection could lead to a renal allograft failure in post-transplant recipients even after a successful histocompatibility match and absence of donor specific preexisting antibody. The tentative possibilities lead to the theory of molecular mimicry as HCMV showed a sequence homology to the ß chain of human histocompatibility complex HLA DR. Therefore, viral peptide could induce antibodies that specifically recognized by human DR ß chain.Thus a regular post-transplant monitoring of HCMV and proper therapeutic intervention is highly warranted in case of renal allograft recipients. Moreover, CMV infection may precipitate acute rejection. Most transplant programs, use routine anti CMV prophylaxis 100 to 200 days.

[*J Indian Med Assoc* 2018; **116**: 52-3 & 56]

Key words **: HCMV, renal transplant, graft dysfunction.**

Human Cytomegalovirus (HCMV) is a member of the herpesvirus group. The transcription of HCMV can be divided into three separate phases: immediate early (IE), early(E) and late (L). From recent research it is now known that during viral latency transcription is restricted to (IE). The products of E and IE are recognized by HCMV specific cytotoxicT lymphocytes. The transcription of IE genes occurs in the absence of viral protein synthesis and is located in restriction areas 0.709 to 0.741 of the genome[1,2,3,4].

Others have reported the sequence homology and immunologic cross-reactivity of HCMVand HLA DR ß chain. Again post-transplant HCMV infection can lead to severe inflammation by elevating production of several inflammatory mediators, triggering immunological cascades and increased expression of MHC. Recent periodicals are well evidenced that there has been strong correlation between HCMV infection and allograft dysfunction and even leading to acute rejection[5,6,7,8].

In our present study we have focused on whether there is an association of post-transplant HCMV infection and clinical manifestation of degraded or dysfunctional renal allograft.

Materials and Methods

In this study the total 28 no of patients with manifestation of cytomegalovirus infection quantified by real time PCR assay and evidenced by histopathology has been included at Medica Superspeciality Hospital, a tertiary care hospital at Kolkata between the years 2015 to 2018.

Real time PCR assay has been done for the quantification of viral DNA from post-transplant recipient's EDTA plasma sample. The assay has been performed by Rotor Gene Q instrument from Qiagen with artus CMV RG RT PCR kit, cat. No. 4503263. To generate the standard curve, positive and negative controls were run along with the patient's sample.

Post-transplant allograft transplant recipients were underwent protocol biopsies to determine allograft dysfunction and rejection.Serum creatinine and total protein assay has been done by standard biochemical procedure.

All statistical analysis has been done by prism 4.1; origin 9.0 and Microsoft excel 2007.

Results

28 post-transplantrecipientsHCMV infected renal allograft recipients had been included in this study. Among those 17 patients are male 11 female. The mean age is 50.81 years. All patients had been evaluated histopathologically for graft degradation and rejection. The recipients had undergone all pre transplant histocompatibility testing and cross matching. There recipients had been screened for other infections and those with only HCMV infection had been included into the study.

Seven patients showed low viral count and no significant difference in graft function. Twelve patients showed moderate infection and again no apparent sign of graft dysfunction. Patients showed high viral load among those and all of them was detected with elevated creatinine and total protein and decreased albumin globulin ratio which

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signifies the deterioration of renal function. One patient lost because of bone marrow depression, retinitis and cmventero-colitis. He presented late in the course with fever and severe diarrhea (Table 1 & Figs 1-4).

Discussion

Recent research reveals that there is an association of post-transplant HCMV infection and worst allograft outcome. HCMV infected post renal transplant recipients showed a deteriorated graft function as the creatinine levels had been seen elevated along with proteinuria. All HCMV infected renal allograft transplant patients were screened for preexisting anti-HLA and non-HLA antibodies prior to transplantation. Therefore chances of donor specific antibody mediated immunogenicity trigger were improbable. Evidences of renal graft dysfunction and degradation had been seen histopathologically and biochemically.

Table 1 — *Total number of patents along with no of male and female and mean age*

Total no of Patients	28
Male	17
Female	11
Mean age	50.81 years
Percentage of patients with high viral load and graft deterioration	32.14%

It is already established that the viral IE and HLA DR Sequences were antigenically identical. Antibody to IE product could react with HCMV infected cells as well as on HLA DRAntigen-positive cells that were not infected with HCMV. The HLA DR and HCMV IE sequences are sufficiently similar and an immune response generated against the virus could also able to react with 'self' HLA DR. The more severe the disease, ie, HCMV replication could generate the greatest response against DR. Additionally, the enhanced micro circulation accompanying the transplanted site could attract lymphoid cells that can be transported to and accumulate at the area of local inflammation[9,10].

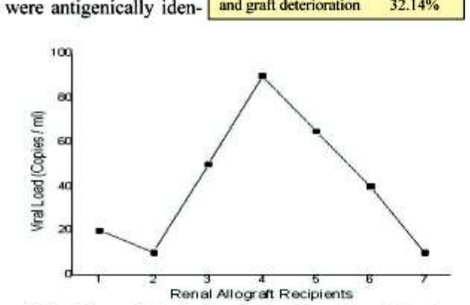

Fig 1 — Line graph showing low viral load in post-transplant renal allograft recipients

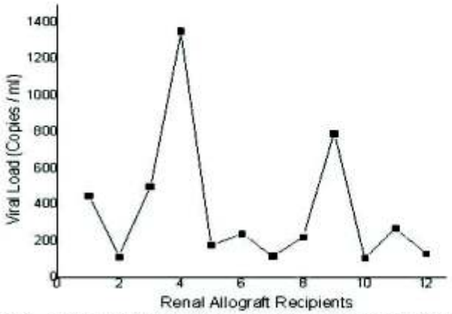

Fig 2 — Line graph showing moderate viral load in post-transplant renal allograft recipients

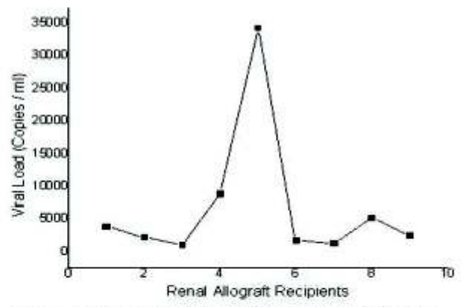

Fig 3 — Line graph showing high viral load in post-transplant renal allograft recipients

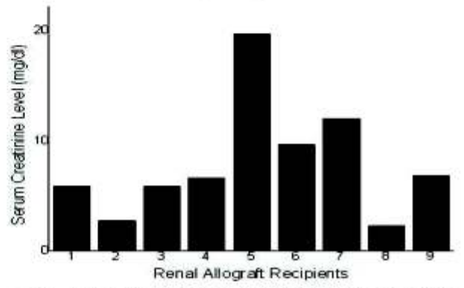

Fig 4 — Bar graph showing the serum creatinine level among patients with high viral load

The sharing of a microbial epitope with a host self-epitope from two dissimilar proteins has been termed molecular mimicry. Molecular mimicry is a common occurrence as judged by analysis of over 600 monoclonal antibodies to a wide variety of DNA and RNA viruses. Some studies showed that 4% of monoclonal antibodies against viruses also reacted with self-determinants[9,10,11].

Conclusion

Our study findings suggested that there is an association between post-transplant HCMV infection and deteriorated renal allograft function. The tentative mechanism behind the degradation of graft tissue and post-transplant

(Continued on page 56)

Original Article

Anticoagulation free hemodialysis

Anupam Majumdar[1], Archana Konar[2], Dilip K Pahari[3]

Anticoagulant is necessary to prevent filter clotting during dialysis. Pleople who are bleeding or likely to bleed need anticoagulant free dialysis. Most centers use regional citrate anticoagulant or intermittant saline flush for intermittant dialysis. Our methos of continus sterile dialysate infusion as prefilter hemo-diafiltration gives benefit of coagulation free dialysis without anti coagulation. There is minimal additional cost, not lobour intensive and very very effective.

[*J Indian Med Assoc* 2018; **116**: 54-6]

Key words **: Heparin free dialysis, hemodiafiltration, pre-filter.**

Hemodialysis (HD) requires extracorporeal blood flow, and antocoagulant esp. heparin have traditionally been used during treatment[1,2]. While this is not problematic for stable outpatients receiving HD, many issues like bleeding from any sources, recent surgery, poly trauma etc. make the use of anti-coagulation during HD a concern. Alternative strategies include heparin-coated dialysis membranes, regeonal heparinization, regeonal citrate anti coagulation, saline flush during dialysisetc[1,2]. While these maneuvers were developed to reduce systemic effects of heparin, saline flush which is commonly used, often led to fiber clottiong[3-9]. In 2000, anti coagulation-free HD protocol based on aggressive intradialytic normal saline (NS) flushing of the dialyzer is routinely used, fiber clotting still occus when technicans fails to fluid flush on time or in patients with hypercoagulable status. To determine the effectiveness of this approach, we have used continuous high volume saline infusion pre filter with equivalent amount of ultrafiltration utilizing online hemodiafiltration machines.

Materials and Methods

A retrospective analysis done on all adults (>18 years) undergoing HD treatments both end-stage renal disease (ESRD) and acute kidney injury (AKI) from June 2018 to September 2018. Patients were excluded from analysis if they received heparin, warfarin or direct thrombin inhibitors or any other antocogulants. A total of 214 HD sessions in 79 patients received high volume pre filter hemodiafiltration without any anticoagulant in the circuit, in patients who needed anticoagulation free HD.

For each HD treatment, the average blood flow rate recorded. In addition, the amount of total pre filter dialysate infusate volumefor each treatment was recorded. Clotting of the circuit was defined by complete or partial clotting requiring replacement of the blood tubing and dialyser till the completion of treatment. We recorded number of treatments had clotting of the dialysis circuit and whether or not this was associated with access type, dialysis treatment blood flow, and flushing volume.

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The Anti Coagulation-free Protocol :

(i) Priming the hemodialyzer with sterile infusion fluid

(ii) Recirculating the sterile infusion fluid until all air has been removed from the bloodlines and hemodialyzer, as is done in 5008 HD series machines automatically,

(iii) During the HD treatment, the hemodialyzer is flushed continuously with huge amount of sterile infusate typically more than 25l in a 4 hour dialysis session. The total volume amount of pre filter sterile infusate fluid depend upon blood flow. Higher the blood flow, more fluid is infused.

(iv) Unless contraindicated, blood flows maximized achieved by access with out complication. Higher the blood flow, there is less chance of clotting.

(v) incidence of clotting partial or complete noted and factors leading to clotting noted.

(vi) Additional fluid infusion given whenever early signs of clotting noted esp. clotting in venous chamber.

(vii) The infused fluid is drained out from the dialyzer at the dialysate out flow line. Therefore, the blood is mixed with sterile infusate fluid throughout dialyzer except terminal portion. Early sign of clotting detected by detecting clotting in the venous chamber while we give pulse saline infusion, clot seen when blood is washed out.

Results

All HD treatments were performed using Fresenius® dialysis machines(5008) compatible with on-line hemodiafiltration. Blood flow was maximized depending on access status. Huge amount (more than 25liter per 4hr. session) of sterile infusion fluid continuously flushing filter instead of intermittent flushing with 100ml normal saline in every 15 mins.The infusate volume is linked with blood flow, higher blood flow, higher infusate volume. This is a problem, since lower blood flow is more prone for clotting. In some selected version of the machines, infusate volume may be selected manually. At any situations, the infusate volume is always higher than manual saline flush. The only advantage of manual flushing is that, we can see the filter and venous chamber during saline flush whether clotting has occurred or not.

Results and Analysis:

Total number of patients was79 and number of total heparin free HDF session was given 214.

In 40 patients had average arterial blood flow less than 250 ml/min in all the sessions and had total 71 session of HDF.

And 39 patients had blood flow more than 250ml/min and got 143 session of HDF.

In the group of patients whose arterial blood flow were less than 250 ml/min their average blood flow was 168 ml/min, and total 15 (21%) sessions needed additional flushing and out of them 5 patients had dialyser clotting and dialyzer were discarded.

Out of 25 (62.5%)patients did not need any additional flushing but 5(20%) patients had minor clotting in the venous chamber and dialyzers were no discarded.

With arterial blood flow less than 250 overall there is 5(7%) had circuit clotting. They needed average substitution pre-dilution flushing volume 14.98 liters with average session length 3.7 hours.

In the group of patients who achieved arterial blood flow more than 250 ml/min their average blood flow was 263.59 ml/min and average per session length was 4.2 hours and average flush volume was 17.33 liters. Additional flushing needed only in 6 (4%) sessions and rest 137 (95.8%) sessions needed no additional flushing. Out of 6 only 1 (0.6%) had dialyser clotting and 142 (99.3%) had no clotting and out of 36 (25%) sessions had no circuit clotting even without additional clotting. Patients with blood flow more than 250 ml/min only 1(0.6%) had dialyser clotting and rest 38(99.3%) patients had no clotting.

Out of 79 patients 41(51.89%) having temporary jugular catheter and 5 sessions in them had circuit clotting; 17(21.50%) had femoral catheter and 5sessions had circuit clotting, 17 (21.50%) had arterio-venous fistula (AVF) and 4(5.06%) had permcath and both group had no circuit clotting.

Discussion

Anticoagulant is an integral part of dialysis, and unfractionated heparin is commonly used. However, for a variety of reasons, anticoagulant free or avoiding systemic effects of it is a necessity. In patients with continuous re-

Parameters	Online hemodiafiltration with pre-dilution blood flow <250 ml /min				Online hemodiafiltration with pre-dilution blood flow ≥ 250 ml /min			
NO. OF PATIENTS	40				39			
TOTAL NO. OF SESSIONS	71				143			
ONLINE prefilter SUBSTITUTION VOLUME per session (approx 4-6 hrs) in liters	14.98 +-1.2				17.33 +- 1.4			
AVERAGE BLOOD FLOW (ml/min)	168+-24				263.59 +-32			
Average session length(hrs)	3.7				4.2			
ADDITIONAL MANUAL FLUSHING	Additional FLUSHING DONE with evidence of venous chamber clotting		Additional FLUSHING NOT DONE as there was no venous chamber clotting		FLUSHING DONE with suggestion of venous chamber clotting		FLUSHING NOT DONE as no evidence of venous chamber clotting	
	15/71=21.19%		56/71-78.8%		6/143=4%		137/143=95.8%	
	CLOTTING	NO CLOTTING	CLOTTING	NO CLOTTING	CLOTTING	NO CLOTTING	CLOTTING	NO CLOTTING
	9(60%)	6(40%)	5(20%)	20(80%)	1(0.6%)	142(99.3%)	0	36(100%)
CIRCUIT CLOTTING leading to discard of dialyzers	CLOTTING		NO CLOTTING		CLOTTING		NO CLOTTING	
	5/71=7%		66/71=92.9%		1/143=0.6%		142/143=99.3%	

nal replacement therapy (CRRT) blood flow is lo may be around 100ml/min, and regional citrate anticoagulation is commonly practised. However, citrate anticoagulation is not freely available in India. In short or prolonged intermittant therapies, where blood flow can be kept 250ml/min or above, intermittant saline flushing is commonly used. The benefit of saline flushing being we can visualize the filter or venous chamber for any clotting. However, there significant number of fibre clotting (historical control) often due to failure of saline flush in time. Loss of dialyzer and blood is significant. In our current protocol, we infuse saline prior to filter 10-25liters in 4-6 hours session compared to 1.5 to 2.5l saline in saline flush mode. In this method, for every patients on anticoagulant free dialysis we give saline flush during dialysis at 15 mins to see fiber or venous chamber clotting. In patients whose blood flow is less <250 ml/min, we continued saline flush every 30 mins in addition to automated pre-dilusional infusion. In patients whose blood flow is more than 250ml/min, if intial slane flush have any indication of clotting, we continue additional flushing. In patients where there was no initial indication of clotting, we continued pre dilutional HDF only. For 25 to 30 liter sinfusion fluid made up from dialysis concentrate and sterile saline, cost increase will be equivant to cost of dialysate concentrate in 4 hr session. To our knowledge, this ie the first report from India about pre filter hemodiafiltration used as totally anticoagulant free dialysis protocol.

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(Continued from page 53)

HCMV infection could be immunogenicity attack and triggering of expression of inflammatory mediators which could lead to successive loss of tissue resulting graft deterioration and dysfunction.

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Observational Study

Peritoneal dialysis, current status and challenges in India

Karthik Balasubramaniam[1], Georgi Abraham[2]

Continuous ambulatory peritoneal dialysis(CAPD) as a renal replacement therapy is practised in India since 1991. Patients with CKD 5 with multiple comorbidities are accepted for CAPD. As dialysis fluid and permanent peritoneal catheters are manufactured in India, this form of renal replacement therapy can be utilised for infants, children, adults and geriatric population. The absolute contraindications are a non-functioning peritoneal and patients with serious cognitive dysfunction. A swan neck catheter with two cuffs is preferred in view of low exit site infection, infective complications such as peritonitis and malnutrition should be prevented by appropriate training and nutritional counselling. We had two patients who lived on CAPD for more than 15 years. Adequacy of dialysis should be ensured by looking at different parameters including Kt/v and physical wellbeing of the patient. Continuous quality improvement (CQI) is mandatory to prevent dropouts.

[*J Indian Med Assoc* 2018; **116:** 57-60]

Key words **: Low middle income country, renal replacement therapy, continuous ambulatory peritoneal dialysis.**

CKD caries enormous economic burden on Low Middle Income Country (LMIC). CKD 5 patients require Renal Replacement Therapy (RRT) which can be offered as a home based therapy in remote places utilizing Continuous Ambulatory Peritoneal Dialysis (CAPD). The absolute requirements for CAPD are a functioning peritoneal cavity, a permanent access and dialysis fluid in different strength and volume in a safe flexible, disposable bag. Renal replacement therapy using CAPD can be offered to any age group and gender who are mentally sound. PD does not require complex machinery and electric power, and the training for the patients and relatives are simple and straight forward. The absolute contraindication for CAPD are only a few - like patients unwilling to do the procedure, non-functioning peritoneum, and cognitive impairment. Ever since CAPD was started in India in 1991 at Chennai by Abraham et al, there had been an increase in the treatment procedure in other parts of India and in other countries of South Asia[1,2]. The local manufacturing of the dialysis fluid and permanent peritoneal catheters, trained professionals including dialysis nurses and technologists, and lately reimbursement policies by various state governments have enabled the growth of CAPD. Peritoneal dialysis has been the choice of RRT in developing countries over last two decades[3]. With its ambulatory nature and freedom from complicated and expensive technology CAPD is the ideal renal replacement therapy for resource limited India. On the other hand, CAPD expansion is limited due to reimbursement issues to the professionals, inadequate government policies, lack of awareness and suboptimal pre dialysis care.

Aims of Chronic Peritneal Dialysis :

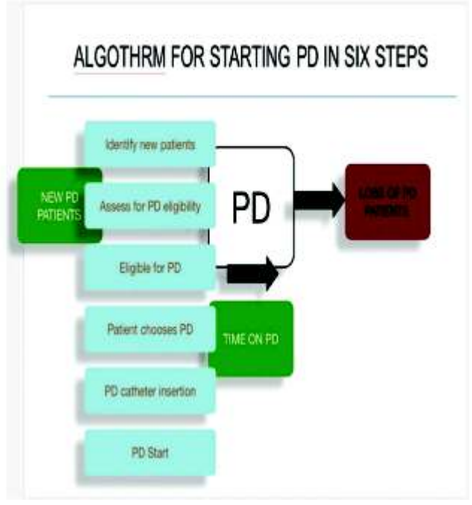
– Reduce morbidity and improve survival

– Improve quality of life compatible with reasonable lifestyle –Prevention of economic hardship of individuals and communities –Adequate socioeconomic support

– Adequate removal of uremic toxins – prevention of uremia –Control of Extracellular Fluid Accumulation

– Prevention / management of anemia, calcium, phosphorus abnormalities, dyselectrolytemia and malnutrition,

Four Reasons for Leaving PD :



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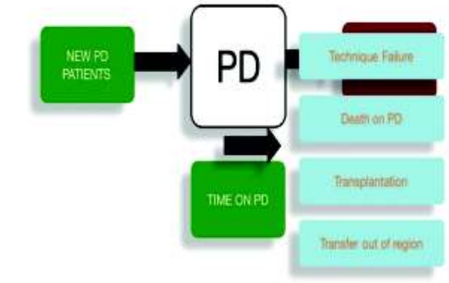
Peritoneal equilibration test (Fig 1) is done at the end



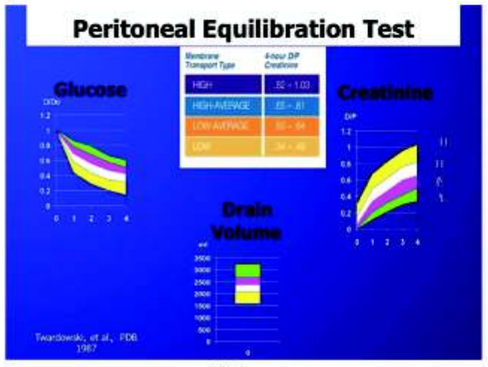


Fig 1 —

of four weeks to know the peritonealmembrane characteristics of individual patients by D/P creatinine AND Glucose absorption[1]. The patients are categorized into high transporters, high average, low average and low transporters. High transporters do well with short dwell exchanges and APD is the treatment of choice. High average and low average transporters are managed by CAPD. Low transporters do well with fluid removal with inadequate solute removal and hence are best treated by Hemodialysis.

CAPD in INDIA :

Continuous ambulatory peritoneal dialysis was initiated in Indian subcontinent in 1991. However the growth of CAPD was restricted by several factors, including patient fears regarding taking responsibility for their own treatment. The most important barrier was the high direct costs engendered by the need to import the fluid bags and the taxes levied by central government. Prices came down substantially in the late 1990s and early 2000s[4] as taxes were removed and by implementing local manufacture of dialysis fluid and lately by cost effective permanent peritoneal dialysis catheters and nationwide networking for supplies. Those changes facilitated expansion of PD programs to all corners of the country.

PD is considered to be the preferred RRT in regions in which ESKD treatment programs are not well-developed and government funding for infrastructure development is limited.

The added advantages – dialysis brought to remote areas and the ambulatory nature of the treatment (requiring less frequent visits to the nephrologist)—make PD ideal for India. However, despite PD having been available for almost 25 years, the modality' penetration remains below 20%. Furthermore, patients are selected for PD not as a matter of choice, but because they are unfit for other modalities of RRT. In a large hospital, only 8% of PD patients were initiated on PD directly; 92% were shifted after being on HD for a mean duration of about 6 months. Of those, two thirds were switched because they tolerated HD poorly, 30% because of comorbid conditions and vascular access problems, and 3% because of lifestyle issues. Patients initiated on CAPD were more likely to have diabetes and coronary artery disease. Currently about 7500 patients in India are on CAPD.

Complications of CAPD :

Complications (Fig 3) related to peritoneal dialysis

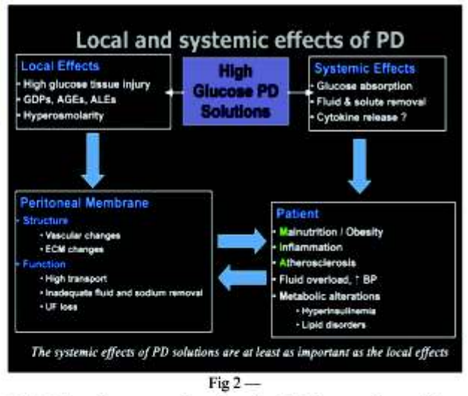


Fig 2 —

(CAPD) catheters are hereby classified as early and late. Early complications arise within the first month after catheter implantation. Complications arising soon after catheter implantation are frequently related to the procedure itself, congenital anatomic abnormalities, and/or to increased intra-abdominal pressure (IAP) generated by infusion of dialysate into the peritoneal cavity. Common complications are Pain, Bleeding at catheter implantation and intraperitoneal bleeding, Bowel perforation, Pericatheter leaks[5], Obstruction, Infections, Herniae, Hydrothorax, Genital edema

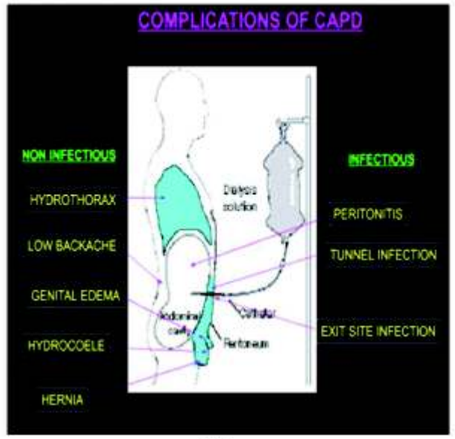


Fig 3 —

Infective Complications :

Exit site infections (ESI) (Figs 5&6), tunnel infections (TI) and peritonitis are the catheter related infections. ESI incidence has remarkably come down by the use of Swan neck configuration (Fig 4) of the catheters manufactured in India, with exit site facing downwards .The treatment of ESI includes appropriate identification of organism, and antibiotic therapy for ten days to two weeks. Anterior nares culture for staph aureus carrier state, removal and replacement of the catheter in the refractory ESI. TI usually accompanies exit site infections, however in the absence of exit site infections ,TI can be diagnosed by using an ultrasound examination of the tunnel (Figs 7&8). If TI is not appropriately treated, this may lead to spread of infection to the peritoneal cavity requiring removal of the catheter and switch over to HD. Peritonitis is rare with disposable double bag technique and most of the instances the organisms are either gram positive or gram negative bacteria which can be successfully treated by intraperitoneal antibiotics. The diagnosis of peritonitis based on (1) abdominal pain, (2) Cloudy effluent, (3) WBC >100 cells with over 50% polymorph nuclear neutrophils (culture positivity) two among the above three is sufficient to make the diagnosis of CAPD peritonitis .One should always be cautious about CAPD procedure and each peritonitis episode the treating team should do a root cause analysis and retraining of the patient with regard to technique. The treatment of peritonitis is identification of the cloudy effluent, immediate intraperitoneal antibiotic therapy[6,7] after sending the first cloudy bag for microbiological examination. Gram stain result can be obtained within a short interval to guide the antibiotic therapy.

Swan Neck Catheter :

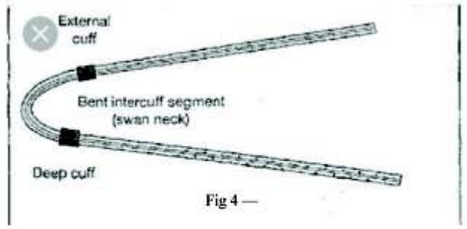


Fig 4 —

Normal Exit Site **Early Infected Site**

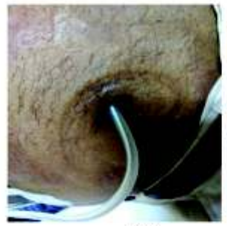
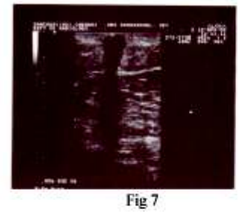


Fig 5

Fig 6

USG ABD Showing Tunnel Infection

Fig 7



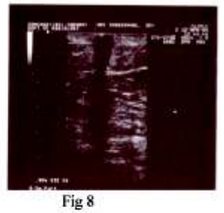


Fig 8

Non-infectious Complications Of Peritoneal Dialysis :

- Hernias
- Genital edema and abdominal wall leak
- Hydrothorax

Other complications to know about :

Encapsulating peritoneal sclerosis, Haemoperitoneum.

Why HD is common in India over CAPD :

More than 90 per cent of the patients are unplanned

quick starters due to presentation to the hospital at a late CKD stage with either anuria or eGfr well below 5ml/min requiring urgent RRT. These patients are urgently initiated on HD using a temporary jugular or femoral access and they have hardly any knowledge of CAPD due to predialysis education and they continue on HD. Firstly, the option of CAPD is rarely offered to patients by a nephrologist. The reasons could be lack of exposure and training in CAPD. HD involves capital expenditure in the form of procurement of machines, water treatment plant etc. and hence financial issues also could cloud the decision making process against CAPD. Secondly, there is a misconception and fear about high infection rates in CAPD. Implementation of disposable double bag systems and patient education and training in CAPD has led to remarkable reduction in peritonitis rates. Thirdly, CAPD is being perceived as the second class form of dialysis since the survival rate was poor in the initial era. It was due to the fact that only the sickest patient received CAPD as a last attempt and the mortality remained high. Lately, with predialysis education, trained nurses and technologists, appropriate nutritional counselling, cardiovascular care, maintenance of residual renal function, patients live longer with good quality of life on CAPD.

Reason for selection of capd over HD :

Home-based therapy of CAPD offers several advantages including preservation of patient autonomy, less number of visits to hospital and improved quality of life with social and professional rehabilitation. The procedure is simple and can be quickly learnt by the patient so that he or she can perform the dialysis herself. CAPD can be undertaken at home with minimal supervision and lesser disruption to normal lifestyle. Patients waiting for transplantation who resides far away where no form of RRT is available, CAPD is a valuable option .As there is scarcity of good quality water, the water consumed per week for three session of HD comes to 360 litres whereas in CAPD the water consumption is much lower at 56 litres per week .The survival of patients during the initial years of dialysis seems to be better with CAPD than HD. The 'down but not out' kidneys seem to preserve their last vestiges of function better while on CAPD than in HD. Various direct and indirect cost calculation in India has given conflicting accounting between the cost of HD and CAPD. While calculating the cost one should also factor travelling cost for HD and time lost per week, post dialysis unwellness hospitalization cost should be taken into consideration between HD and CAPD.

Vercoming the Challenges In PD in India :

The formation of peritoneal dialysis society (PDSI) of India in 1997 , annual congress of PDSI, CAPD training for young nephrology trainees , Indian journal of peritoneal dialysis (IJPD), special training for nurses and technologies during the annual congress are all positive moves in propagating and spreading CAPD in south Asian region. To overcome the challenges to establish CAPD as a better choice of RRT, apart from nephrologists, government of India should take initiatives in helping more number of patients to be able to access therapy. The government can abolish the VAT/GST taxes on PD fluid bag. Similar to HD, peritoneal dialysis can also be brought under insurance scheme. The government should realise that PD is the safe, efficient, practical and patient friendly RRT for India.

Conclusion :

CAPD is safe, efficient and patient-friendly form of RRT which can be done as a home therapy as contraindications are very limited and advantages are many. It is a lifesaving form of renal replacement therapy for diverse age group from neonates to old age and without any gender, differences although countries like Thailand, Philippines and Vietnam are economically behind us, but the number of PD users and the government schemes are way ahead.

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Observational Study

Prevalence of urinary tract infection among pregnant women in a tertiary care hospital in West Bengal

Nasifa Hassan[1], Soumen Saha[2], Sudip Roy[3], Somnath Laha[4], Kumkum Pahari[5]

Urinary tract infection is one of the most commonly diagnosed infections in pregnancy. Common causative organisms are Gram Negative Bacilli like Escherichia coli, Klebsiella sp. or Gram-positive bacteria like Enterococcus and Staphylococcus. Identification of uropathogens and their treatment is necessary for the viability of fetus.

[*J Indian Med Assoc* 2018; **116:** 61-2]

Key words **: UTI, Pregnancy, Renal failure, antibiotics.**

Urinary Tract Infection (UTI) is one of the most commonly diagnosed infections. It can be defined as isolation of an organism from urine culture in quantitative or semi-quantitative counts of $\geq 10^5$ cfu/ mL or as more than 100 organisms per 100 mL of urine with accompanying pyuria in a symptomatic patient[1]. Clinical manifestation of UTI depends upon the anatomic area involved, causative organism, and severity of infection, host immune response etc. Common symptoms are pain or burning sensation during micturition, increased frequency of micturition, feeling of urgency, passage of blood in urine or cloudy urine, lower abdominal pain and fever. Common causative agents of UTI are Gram negative bacilli like Escherichia coli, Klebsiella sp, or Gram positive bacteria like Enterococcus and Staphylococcus[2-4]. Incidence of UTI is higher in women than men, 40% to 50% of whom will suffer at least one clinical episode during their lifetime[5]. Pregnant women are prone to develop UTI than non-pregnant. During pregnancy due to compression of ureters by gravid uterus, ureteral dilation leads to stasis of urine. Bladder tone also reduces in pregnancy. Vesico-Ureteric reflux, past UTI, diabetes mellitus, hyperuricemia also are important predisposing factors for UTI[6-8].

The aim of the study is to detect prevalence of UTI among pregnant women attending this tertiary care center and its distribution in relation to age, parity and gestational age of pregnant women and identification of uropathogens and their antibiotic sensitivity pattern for effective treatment.

Materials and Methods

Study site and period — the study was conducted at Medica super specialty Hospital, Kolkata between Feb 2018 to Sept 2018.

Medica Superspeciality Hospital, Kolkata 700099
[1]MSc, scientific officer, Molecular lab
[2]MD, Senior Registrar, Microbiology
[3]MD, Consultant, Microbiology
[4]MD, Professor and consultant Obstetrics and Gynecology
[5]MD, senior consultant Obstetrics and Gynecology

Sample size — total 422 pregnant women who have delivered their baby in this hospital during the specified period with or without symptoms of UTI were included in this study.

Exclusion criteria — who were already on antibiotics and improperly collected or stored sample.

Isolation and identification of uropathogens — clean cached urine samples were collected in sterile container and processed within 2 hours, where delay more than 2 hours anticipated samples were stored in 2-80 C for maximum 6 hours. Samples were inoculated in CLED agar with calibrated loops following standard inoculation methods. Cultures were read after 24 hours of aerobic incubation at 370 C, only cultures with 105 colony count or above were further processed for identification. Identification of the isolated organism was done using automated system BD Phoenix 100.

Antimicrobial sensitivity data — Isolated organisms further processed to obtain the antibiotic sensitivity pattern. Antibiotic sensitivity done by using automated system BD Phoenix 100. Antibiotic sensitivity of Group B Streptococcus was done by modified Kirby Bauer method using MHA containing 5% sheep blood.

Results

- Out of 422 pregnant women evaluated, prevalence of UTI was found to be 21.80%, Table 1 showing the prevalence rate.
- Prevalence of UTI in relation to age of the pregnant women has been shown in Table 2. Highest incidence has been found in the age group of 25 to 30 years.
- Table 3 showing relationship of UTI with number ofgravida. Highest incidence of infection is seen in primigravida.
- Incidence of UTI in relation to gestational age has

been shown in Table 4. Women in their last trimester has greater incidence of UTI 52.17%.

Table 1 — *Prevalence rate of UTI*

Total no of pregnant	Total no of positive UTI
422	92 (21.80)

- Among the 92 bacterial isolates majority are Gram negative bacilli, only 10.87% Gram positive cocci was isolated as a causative agent of UTI in pregnant women. Among the Gram negative bacteria Escherichia coli was the most frequent isolate 59.81%, followed by Klebsiella pneumonia 18.47% and Proteus mirabilis 10.86%. Gram positive cocci isolated were Enterococci 8.69% and Group B Streptococcus 2.17% as shown in Table 5.

Table 2 — *Distribution of UTI according to age*

Age	No of patients	No of positive cases
<20 years	12(2.84)	1(1.08)
20-25 years	168(39.81)	38(41.30)
25-30 years	208(49.28)	50(54.34)
>30 years	34(8.05)	3 (3.26)

Table 3 — *Distribution of UTI according to gravida*

Gravida	No of patients	No of positive cases
Primi gravida	208	55(26.44)
Second gravida	196	35(17.85))
Third gravida and above	18	2(11.12)

- Antibiotic sensitivity pattern to commonly used drugs were determined from the isolated organisms. All the Gram-negative isolates were sensitive to Amikacin and Carbapenoms. Sensitivity to Nitrofurantoin was high in E. coli than Klebsiella. Sensitivity to Fluroquinolones is altogether low in Gram negative bacteria isolated. Antibiotic sensitivity result has been shown in Table 6 & 7.

Table 4 — *Distribution of UTI according to gestational age*

Trimester	No of cases
1st	30(32.6)
2nd	14(15.22)
3rd	48(52.17)

Table 5 — *Frequency of Bacteria causing UTI among pregnant women*

Etiological agent	No of cases
Escherichia coli	55(59.81)
Klebsiella	17(18.47)
Proteus	10(10.86)
Gr B streptococcus	2(2.17)
Enterococcus	8(8.69)

- Table 8 showing relationship of UTI cases with birth weight of baby. Incidence of UTI is little more 25.64% in women who have given birth to low birth weight babies.
- During the specified study period there were 5 twin deliveries.Among which 2 mothers had developed UTI, making the percentage of UTI in twin pregnancies higher 40% as shown in Table 9.

Discussion

In this study we have found that the prevalence of UTI is considerably significant among individuals with last trimester pregnancy. *E coli* has been detected as the most common causative organism. Other organisms include gram negative Klebsiella, Proteus and gram positive Enterococcus and Streptococcus. Fluoroquinolones has been evidenced the less sensitive drug and nitrofurantoin possible the drug of choice in case of infection of *E coli.* It has also been observed that incidences of UTI among pregnant women who has twin pregnancy is considerably higher than single which again supports the pathophysiological events causing UTI in pregnancy.

Other studies have also shown that predominant uropathogen is *E coli* and the infection rate if higher in the last trimester due to progressive obstruction, stasis of urine due to ureteral dilation, reduced bladder tone, Vesico-Ureteric reflux, history of past UTI, diabetes mellitus and hyperuricaemia.

Table 6 — *Antibiotic sensitivity pattern – Gram negative bacilli*

Antimicrobials	E coli	Klebsiella	Proteus
Penicillin	1(1.82)	0(0)	-
Cephalosporin	18(32.73)	5(29.41)	8(80)
Amikacin	55(100)	17(100)	10(100)
Meropenum	55(100)	17(100)	10(100)
Ciprofloxacin	12(21.82)	7(41.17)	8(80)
Levofloxacin	12(21.82)	7(41.17)	8(80)
Nitrofurantoin	54(98.2)	12(70.59)	-
Co- trimoxazole	28(50.9)	15(88.23)	9(90)

Table 7 — *Antibiotic sensitivity pattern – Gram positive cocci*

Antimicrobials	Enterococci	Gr B Streptococci
Penicillin G	2(25)	2(100)
Amoxy-clav	-	2(100)
Vancomycin	8(100)	2(100)
Teicoplanin	8(100)	2(100)
Linezolid	8(100)	2(100)
Erythromycin	5(62.5)	2(100)
High load Gentamicin	8(100)	-

Table 8 — *Distribution of UTI according birth weight of baby*

Birth weight	No of deliveries	No of positive cases
<2.5 kg	117	30(25.64)
2.5-3 kg	301	62(20.6)
>3 kg	4	0

Table 9 — *Relation of UTI with type of pregnancy*

Type of pregnancy	No of positive UTI cases
Twin pregnancies - 5	2(40)
Single pregnancies - 417	90(21.6)

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Activities Report

IMA Perinthalmanna Branch Organised State Working Committee of IMA KSB, Conference 'Kollamcon 2018' at Kollam, World Diabetic Day with Exhibition at Moulana Hospital, Introduction Class on 'COLS' for the Driving Licence Applicants, Health Education Class at PTM College, Observe National Epilepsy Day, Live TV Programme, On 17 & 18th November, 2018 Central Working Committee at Indore, 'Child's Rights Week' Observation, Bone Mineral Density Assessment and Health Check Up for the Elderly at Pain and Palliative Care Clinic, World Diabetes Day Symposium on SGLT Inhibitors and CV Safety, On all Wednesdays Free Clinic For Elderly Patients at Pain and Palliative Care Clinic

IMA Madhya Kerala Branch Observed Executive Committee Meeting, Women Empowerment and Rehabilitation Programme, Conference KOLLAMCON, World Diabetes Day, Children's Day Celebrated on 14/11/2018, National Epilepsy Day on 17/11/2018, Free Gynaecological Medical Camp, Anaemia detection camp and Basic Life Support Training for Students, Family Meet of Volunteers and Patients of Palliative Care, Workshop on Antibiotic and Geriatric problems for JPNHs, Asha Workers, Ward members from Panchayaths near Kolanchery

IMA Trivandrum Branch organised WIMA executive meeting, Palliative Care Monthly Review Meet, Cancer Detection Camp at Chappath, World Diabetes Day, Children's Day, Organ Donation programme, Breast cancer detection camp, conducted an essay competition for nursing students, Handed over Medical kit to Police Control Room, Inauguration of IMA Pavilion at Ananthapuri Fest

IMA Tirurangadi Branch organised GB meeting and CME programme

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