

Efficacy of 2.5% and 1.25% Povidone-Iodine Solution for Prophylaxis of Ophthalmia Neonatorum

Faisal Aziz Khan¹, Muhammad Ashraf Hussain², Shafaq Pervez Khan Niazi⁴, Zia ul Haq³ and Naveed Akhtar⁵

ABSTRACT

Objective: To determine the efficacy of 2.5% and 1.25% Povidone-Iodine solution for *Ophthalmia neonatorum* prophylaxis.

Study Design: Interventional study.

Place and Duration of Study: Eye Department, Combined Military Hospital, Sargodha, from May to November 2014.

Methodology: A total of 200 eyes of 100 newborn babies were enrolled and divided into two groups of 100 right eyes and 100 left eyes. A conjunctival swab for bacterial culture was taken within 30 minutes after delivery. A single drop of 2.5% Povidone-Iodine was then placed in the right eye while in the left eye a single drop of 1.25% Povidone-Iodine was placed. Thirty minutes after placing Povidone-Iodine, a conjunctival swab was again taken. A bacterial suspension was prepared from each swab in determining bacterial counts. The bacterial suspension was inoculated on yeast extract agar and the number of colony forming units were counted. At each culture, the number of colony forming units before and after instillation of 2.5% Povidone-Iodine and 1.25% Povidone-Iodine were compared. Wilcoxon's signed rank test was used for statistical analysis.

Results: The 2.5% Povidone-Iodine solution caused a statistically significant decrease in the number of colony forming units ($p=0.001$). Similarly, the 1.25% Povidone-Iodine solution also reduced the number of colony forming units to a statistically significant level ($p=0.001$).

Conclusion: The 1.25% concentration of Povidone-Iodine is as effective as the 2.5% concentration of Povidone-Iodine in reducing the number of colony forming units in healthy conjunctivae of newborns.

Key Words: *Ophthalmia neonatorum*. Prevention and control. Povidone-Iodine.

INTRODUCTION

Worldwide approximately 10,000 newborns become blind annually with *Ophthalmia neonatorum* (ON).¹ In the developing world, ON is still a very common threat to vision. In India, the prevalence varies from 0.5 - 33%, depending on the socio-economic status of the region.² In Pakistan, the frequency of ON in hospital delivered babies is reported to be 17%.³

The most important bacterium causing damage to vision is *Neisseria gonorrhoea*.¹ In the absence of adequate prophylaxis, 30% to 42% infants born by vaginal delivery to infected mothers develop gonococcal ON.⁴ Despite a decrease in frequency throughout the world, the consequences of untreated ON remain grave.⁴

World Health Organization (WHO) launched an action plan in 1999 for low income countries, titled "Vision 2020: The Right to Sight". One of the strategies includes ocular prophylaxis of newborns to prevent ON so as to

eliminate one of the avoidable causes of blindness in children.⁵ In Iran, Khoshdel *et al.* showed a high incidence of gonococcal and chlamydial conjunctivitis recommending that neonatal prophylaxis must be initiated promptly.⁶ In Pakistan, currently there is no routine practice of prophylaxis of ON, especially at a national level, and one of the reasons is the scarcity of available data whose results could be applied to the mass population.³

Several chemical agents have been used for the prophylaxis of ON including erythromycin, tetracycline and silver nitrate.⁷ Silver nitrate has now been abandoned in several countries (e.g., USA) and replaced with 0.5% erythromycin and 1% tetracycline ointment.⁸ Erythromycin and tetracycline are only relatively effective against *Chlamydia*. In case of *Neisseria gonorrhoeae*, beta-lactamase producing strains have emerged and the effectiveness of tetracycline and erythromycin as topical prophylactic agents against these strains is questionable.⁹ Recently, the 2014 WHO report on antimicrobial resistance has highlighted that in 36 countries decreased resistance of *Neisseria gonorrhoeae* to third-generation cephalosporins has been verified.¹⁰

Outbreaks of antibiotic resistant bacterial conjunctivitis in neonates, prompted researchers to look for a new prophylactic agent that would be effective against the most common etiologic pathogens without causing resistance.⁷ A pilot study was conducted to determine

¹ Department of Ophthalmology / Pathology Lab² / Pediatrics³, Combined Military Hospital, Sargodha.

⁴ Department of Ophthalmology / Anatomy⁵, Rai Medical College, Sargodha.

Correspondence: Dr. Faisal Aziz Khan, Consultant Ophthalmologist, Department of Ophthalmology, Combined Military Hospital, Sargodha.

E-mail: faisaleyecare@gmail.com

Received: March 16, 2015; Accepted: November 03, 2015.

the efficacy of 2.5% Povidone-Iodine (PVP-I) by measuring the decrease in the number of bacterial colony forming units and then its effectiveness as a prophylactic agent was evaluated by recording the incidence of ON in a multi-year trial.⁷

PVP-I is effective against bacteria, fungi, *Chlamydia*, *Herpes simplex virus-2* (HSV) and Human Immunodeficiency Virus (HIV). When used as a 2.5% solution, it is well-tolerated by the sensitive eyes of neonates. The conjunctiva turns brown after instillation indicating adequate application. The cost of PVP-I is affordable and the absence of true antimicrobial resistance to the compound should be a key factor in encouraging its use.¹⁰

The rationale of the study was lack of data regarding the effectiveness of the previously used 2.5% concentration and specifically the newer less toxic 1.25% concentration PVP-I in neonates.

The objective of this study was to determine the effectiveness of 1.25% concentration of PVP-I versus 2.5% for the prophylaxis of ON in healthy conjunctivae of the newborns.

METHODOLOGY

This interventional study was conducted at the Neonatal Intensive Care Unit (NICU) of Combined Military Hospital, Sargodha, from May to November 2014. Two hundred eyes of 100 consecutive newborn babies delivered at CMH, Sargodha who met the selection criteria, were enrolled. The sample size was selected on the basis of the 17% incidence of *Ophthalmia neonatorum* in Pakistan in a hospital based setting³ by applying the formula $n = (z_{1-\alpha/2} \epsilon)^2$ using the WHO calculator at a confidence interval (1- α) of 90% and relative precision ϵ 0.17. The study included newborns that were delivered after 37 weeks of gestation, with a birth weight of 2.0 kgs or more and through both mode of deliveries whether caesarean or vaginal. Newborns who had any obvious ocular malformations, eyelid malformations or their mother was unable to bring the baby back to the hospital in case conjunctivitis developed, were excluded from the study. The study was approved by the institutional Ethical Committee.

Povidone-Iodine solution was prepared in two different concentrations of 2.5% and 1.25%. Before instilling Povidone-Iodine drops, a conjunctival swab was taken from each eye using two separate sterile stick swabs from a clear sterile labelled plastic bottle. A written informed consent was obtained from each child's mother for taking the swab and placing Povidone-Iodine drops. The swab was swepted in the lower fornix from the inner canthus to the outer canthus taking care not to touch the eyelids. The swabs from each eye were then placed back in the same container and sent immediately to the laboratory for bacterial culture. After taking conjunctival swab, the right eye of each new born was instilled with a single drop of 2.5% and left eye with 1.25% Povidone-Iodine, respectively. Thirty minutes

after receiving Povidone-Iodine drops, a conjunctival swab was taken again from each eye under same measures as described previously and sent to the laboratory immediately for bacterial culture.

In the laboratory, each swab was immersed in 2 ml of sterilized distilled water and rotated for about 30 seconds each in clockwise and anticlockwise directions to make an even bacterial suspension. One ml of the suspension was utilized in determining bacterial counts using the Plate Count method. The remaining quantity was saved for retesting, if required, or making serial dilutions in case of obtaining a very high bacterial count limiting the possibility of direct counting. This specimen was kept at refrigerated temperature till its use. For counting exactly 1 ml of undiluted specimen was aseptically dispensed using pipette to each of the sterile disposable Petri dishes/Culture plates. Fifteen ml of freshly prepared and sterilized molten yeast extract agar at around 50°C was poured over each dispensed suspension and the plates rotated clockwise and anticlockwise to make even distribution of the suspension within molten agar. The plates were then incubated at 37°C for 48-hour. At the end of incubation period, all the Colony Forming Units (CFUs) were counted in good light. The procedure was repeated for the plates giving very heavy counts (> 200 CFUs/plate) after appropriate dilutions of the preserved suspension.

The mode of delivery, gestational age, birth weight and gender was recorded. The babies remained admitted in NICU for the next 24 hours for observation and the mothers were instructed to report to the nursing staff, if there was redness or discharge from the eyes.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive statistics were used to describe the clinico-demographic data. Frequency and percentages were calculated for qualitative variables. Median \pm interquartile range (IQR) were used for numerical data. Wilcoxon signed rank test was selected for comparing the colony forming units count before and after instillation of 2.5% and 1.25% Povidone-Iodine eye drops. A p-value < 0.05 was considered statistically significant.

RESULTS

The male to female ratio was 1:1. Birth weight ranged from 2.2 to 4.1 kgs with a mean value of 3.05 \pm 0.41 kg. Three babies (3%) developed conjunctival hyperaemia in the right eye soon after instillation of a 2.5% PVP-I; whereas, in the left eye in which 1.25% PVP-I was placed none developed conjunctivitis. Chemical conjunctivitis was not detected at the 24-hour determination point in either eye in any of the babies.

In right eye in which 2.5% PVP-I was instilled, the median \pm IQR of colony forming units before instilling PVP-I was 4.00 (149.0) which reduced to 1.00 (8.00) after the effect of PVP-I as mentioned in Table I. This decrease in the number of CFU was statistically

Table I: Comparison of colony forming units before and after instillation of 2.5% PVP-I drops (n=100).

Colony forming units	Before (n=100)	After (n=100)	p-value
Median (IQR)	4.00 (149.00)	1.00 (8.00)	< 0.001

Table II: Comparison of colony forming units before and after instillation of 1.25% PVP-I drops (n=100).

Colony forming units	Before (n=100)	After (n=100)	p-value
Median (IQR)	5.50 (171.50)	1.00 (4.00)	< 0.001

significant ($p < 0.001$). In the left eye after the instillation of 1.25% PVP-I drops, the number of CFU decreased to the median value of 1.00 (4.00) from 5.50 (171.50) which was before the instillation of PVP-I as mentioned in Table II. This reduction in the number of CFU was statistically significant ($p < 0.001$).

DISCUSSION

In this study, the efficacy and adverse effects of two different concentrations of PVP-I namely 2.5% and 1.25% were evaluated on the healthy conjunctiva of newborns. The ophthalmic solution of PVP-I ranges from 1.25% to 5%. This dilution is tolerated well without irritating the sensitive eyes of neonates and is relatively non-toxic compared to a 5% solution of PVP-I which occasionally produces conjunctival redness.^{10,11} The 5% solution of PVP-I is only suitable for use after application of a local or topical anaesthetic due to its stinging effect. Therefore, its use is only recommended for prophylaxis before surgery.¹² With the 2.5% PVP-I solution used in this study, it was found that only three babies (0.03%) developed conjunctival congestion soon after instillation of the drop. This low frequency of conjunctival irritation suggests that the 2.5% concentration of PVP-I is not harmful to neonate's eyes.

Some authors have reported that the 2.5% concentration of PVP-I caused severe burning in the eyes for 30 minutes and, therefore, compliance with the 2.5% concentration may be low. The 1% solution is better tolerated without pain,^{12,13} and also the 1% solution is included in the WHO manual eye drops update 2002 for use in bacterial conjunctivitis.¹² Based on these reports, the 1.25% PVP-I was evaluated and found that none of the babies developed conjunctival hyperaemia after instillation which further augments the previous findings that the 1.25% is more comfortable for the babies. Richter found that the 1.25% concentration did not derange the physiological levels of thyroid stimulating hormone and iodine levels in the urine in healthy newborns. Moreover, no systemic side effects with 1.25% PVP-I have been reported in the literature.^{14,15} In this study, systemic side effects of either of the 2.5% or 1.25% concentrations of PVP-I in babies were not evaluated.

The time duration after delivery for application of prophylaxis is recommended to be soon after birth upto

one hour for gonococcal ophthalmia; as delaying upto one hour does not impair the prophylactic agent's efficacy.¹⁶ Specifically for PVP-I, its application 24 hours after birth does not provide further benefit for prophylaxis against ON.¹⁷ All these babies received prophylaxis with PVP-I within the first hour after birth.

The Canadian Paediatric Society recommends that the eye should not be irrigated after instilling the prophylactic agent as it may reduce the efficacy and probably not decrease the incidence of chemical conjunctivitis.¹⁶ The authors did not irrigate the PVP-I solution from the conjunctival sac.

A single drop of an effective prophylactic agent is considered the best way for prophylaxis.¹⁷ The application of a second drop of PVP-I in the first post-natal day is of no additional benefit, rather it increases the incidence of eyelid edema.¹⁸ The authors, therefore, instilled only a single drop of 2.5% or 1.25% PVP-I to cause less discomfort to the babies' eyes without compromising on the efficacy.

All the babies included in this study were delivered by caesarean section. Verma *et al.* and Isenberg *et al.* found that the incidence of conjunctivitis was almost the same among babies delivered by vaginal or caesarean section.^{19,20} Verma *et al.* found no correlation between the microbiology of the conjunctival swabs of the infected eyes where *Staph aureus* was the commonest isolate, and the vaginal and cervical swabs of the mothers in which *Escherichia coli* was the commonest isolate. On the basis of his findings, he then suggested that neonatal conjunctivitis is more likely to be acquired postnatally.²⁰ Similarly, in Pakistan Shireen *et al.* found caesarean section to be a statistically significant risk for neonatal conjunctivitis versus spontaneous vaginal delivery and attributed the cause to unhygienic practices during handling of the newborn.³ The Canadian Paediatric Society recommends that prophylaxis be given to babies after caesarean section as infection has also been reported with this mode of delivery.¹⁶ Based on this data, the authors strongly suggest that the prophylaxis should continue to be offered to babies born by caesarean section also.

Among the risk factors for conjunctivitis, prematurity, low birth weight and abnormal vaginal presentation were identified. But out of these three factors, only abnormal vaginal presentation was found to be an independent predictor for conjunctivitis.²¹ Ranjit *et al.* found premature rupture of membranes as a leading maternal risk factor for ON but with the mother having a sexually transmitted disease; and also reported a low Apgar score on the neonatal side for increasing the risk of conjunctivitis.²² Shireen *et al.* did not find a statistically significant relationship of either the gestational age or low birth weight with neonatal conjunctivitis.³ In this study, neither of the above mentioned risk factors affected the outcome as all babies were delivered after 37 weeks of gestation with a birth weight of 2.5 kgs or more and normal Apgar score.

Chemical conjunctivitis is a known side effect of silver nitrate.⁸ PVP-I and erythromycin cause a statistically significant lesser toxicity after 24 hours of instillation than silver nitrate.¹¹ In this study, none of the eyes developed chemical conjunctivitis after a 24-hour period either with 2.5% or 1.25% concentration of PVP-I.

PVP-I in a concentration of 2.5% when compared with the two commonly used agents erythromycin and silver nitrate, causes a more significant decrease in the number of colony forming units and bacterial species in a normal healthy conjunctiva.¹¹ Isenberg *et al.* reported that 2.5% PVP-I is statistically more effective for prophylaxis against ON than erythromycin and silver nitrate.¹⁹

In Manila, Philippines, 1.25% PVP-I was used four times a day for the treatment of bacterial conjunctivitis and was found to be as effective as antibiotic combination (neomycin-polymix in B-gramicidin) for curing bacterial conjunctivitis and marginally more effective than the antibiotic combination for treatment of chlamydial conjunctivitis.²³ After reviewing the research work done on prophylaxis for ON, Darling *et al.* has suggested that PVP-I and erythromycin is more effective than silver nitrate in the prevention of chlamydial ophthalmia neonatorum.²⁴

Regarding postoperative use after 24 hours of ocular surgery, the 2.5% solution of PVP-I significantly reduces the number of CFUs while the antibiotic combination of neomycin-polymixin B-gramicidin does not.²⁵ PVP-I in 2.5% or 1.25% concentration has also been used successfully postoperatively for the prevention of ocular infection and has similar efficacy to the antibiotic combination of neomycin-polymixin B-gramicidin.²⁵ The present results mirror the results of the previously published data in which both 2.5% and 1.25% concentration of PVP-I caused a statistically similar significant reduction in the number of CFUs. However, this study is the first of its kind internationally in which the 1.25% concentration of PVP-I has been analyzed specifically in newborns for prophylaxis of ON and found to be equally as effective as the 2.5% concentration.

CONCLUSION

A single drop of 1.25% PVP-I given within the first hour of delivery is as effective as the 2.5% concentration. Taking the efficacy and adverse effects into consideration, the 1.25% concentration of PVP-I is the more appropriate concentration for neonatal eye prophylaxis.

REFERENCES

1. Iyamu E, Enabulele O. A survey on *Ophthalmia neonatorum* in Benin City, Nigeria (Emphasis on *Gonococcal ophthalmia*). *Online J Health Allied Scs* 2003; **2**:2.
2. Wadhvani M, D'souza P, Jain R, Dutta R, Saili A, Singh A. Conjunctivitis in the newborn- a comparative study. *Indian J Pathol Microbiol* 2011; **54**:254-7.
3. Gul SS, Jamal M, Khan N. Ophthalmia neonatorum. *J Coll Physicians Surg Pak* 2010; **20**: 595-8.
4. Zuppa AA, D'Andrea V, Catenazzi P, Scorrano A, Romagnoli C.

5. Global initiative for the elimination of avoidable blindness, action plan 2006-2011 WHO press 2007 :23.
6. Khoshdel A, Taheri S, Khadivi R, Saedi E. Imani KAR, Jazaeri F. Incidence and bacteriological profile of neonatal conjunctivitis in Hajar Hospital, Shahrekord, Iran. *Iran J Pathology* 2012; **7**: 86-91.
7. Gomi CF, Granet DB. Common conditions affecting the external eye. In: Wilson ME, Saunders RA, Trivedi RH, editors. *Pediatric ophthalmology current thought and practical guide*. Springer-Verlag Berlin Heidelberg, 2009 .p. 4522.
8. Schaller UC, Klauss V. Is Crede's prophylaxis for *Ophthalmia neonatorum* still valid? *Bull World Health Organ* 2001; **79**.
9. Zar HJ. Neonatal chlamydial infections: prevention and treatment. *Paediatr Drugs* 2005; **7**:103-10.
10. Meyer D. *Ophthalmia neonatorum* prophylaxis and the 21 st century antimicrobial resistance challenge. *Middle East Afr J Ophthalmol* 2014; **21**:203-4.
11. Isenberg SJ, Apt L, Yoshimori R, Leake RD, Rich R. Povidone-iodine for *Ophthalmia neonatorum* prophylaxis. *Am J Ophthalmol* 1994; **118**:701-6.
12. Bolt A. Povidone-Iodine. *Community Eye Health* 2003; **16**:63.
13. Kranabtl HP, Bichler A. Prophylaxe *Ophthalmia neonatorum*. *Hyg Monitor* 2001; **7**:2-3.
14. Kramer A. New aspects in prophylaxis of *Ophthalmia neonatorum* (Crede Prophylaxis). *Wein Klin Wochenschr* 2002; **114**:171-2.
15. Richter R, Below H, Kadow I, Kramer A, Müller C, Fusch C. Effect of topical 1.25% povidone-iodine eyedrops used for prophylaxis of *Ophthalmia neonatorum* on renal iodine excretion and thyroid-stimulating hormone level. *J Pediatr* 2006; **148**:401-3.
16. Embree J. Recommendations for the prevention of neonatal ophthalmia. *Paediatr Child Health* 2002; **7**:480-83.
17. Abazi F, Kubati M, Berisha B, Gashi M, Kocinaj D, Krasniqi X. *Ophthalmia neonatorum*. In: Pelikan Z editor. *Conjunctivitis-A complex and multifaceted disorder*. Intech 2011.p.157.
18. Isenberg SJ, Apt L, Del Signore M, Gichuhi S, Berman NG. A double application approach to *Ophthalmia neonatorum* prophylaxis. *Br J Ophthalmol* 2003; **87**:1449-52.
19. Isenberg SJ, APT L, Wood M. A controlled trial of Povidone-iodine as prophylaxis against *Ophthalmia neonatorum*. *N Engl J Med* 1995; **332**:562-6.
20. Verma M, Chhatwal J, Varughese PV. Neonatal conjunctivitis: a profile. *Indian Pediatr* 1994; **31**:1357-61.
21. Spaans WA, Knox AJ, Koya HB, Mantell CD. Risk factors for neonatal infection. *Aust NZ J Obstet Gynaecol* 1990; **30**: 327-30.
22. Ranjit R, Menezes L, Drucker M, Msukwa G, Batumba N. Maternal and neonatal risk factors associated with vertical transmission of *Ophthalmia neonatorum* in neonates receiving health care in Blantyre, Malawi. *Middle East Afr J Ophthalmol* 2014 ; **21**:240-3.
23. Isenberg SJ, Apt L, Valenton M, Del Signore M, Cubillan L, Labrador MA, *et al.* A controlled trial of povidone-iodine to treat infectious conjunctivitis in children. *Am J Ophthalmol* 2002; **134**:681-8.
24. Darling EK. A meta-analysis of the efficacy of ocular prophylactic agents for the prevention of *Gonococcal* and *Chlamydial*, *Ophthalmia neonatorum*. *J Midwifery Womens Health* 2010; **55**:319-27.
25. Isenberg SJ, Apt L. The ocular application of Povidone-Iodine. *Community Eye Health* 2003; **16**:30-1.

