Erythromycin Prophylaxis for Neonatal Conjunctivitis: Ointment versus Drops

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ABSTRACT: **Background:** Due to a shortage of individualized erythromycin ointment (IEO), we switched to shared erythromycin drops (SED). Following this change, nurses claimed observing more cases of eye discharge.

Objectives: To test whether switching from IEO to SED affected the rate of neonatal conjunctivitis (NC).

Methods: The study group included 14,916 neonates › 35 weeks of gestation, further divided into two birth periods of 12 months each: 1 January 2013 to 31 December 2013 (IEO) and 1 February 2014 to 31 January 2015 (SED). We compared the two birth periods with regard to three variables: clinical NC (number of conjunctival swabs/1000 neonates), bacterial NC (number of culture-positive swabs/1000 neonates), and bacterial growth percentage (number of culture-positive swabs/100 samples).

Results: Compared to 2012–2013, the period 2014–2015 included fewer cesarean deliveries and shorter length of stay (LOS). Clinical NC, bacterial NC and bacterial growth percentage were not different between the two periods. Variables that were independently significantly associated with increased clinical NC included male gender (OR 1.48, CI 1.21–1.81) and LOS (OR 1.24, CI 1.18–1.29). LOS was associated with bacterial NC (OR 1.19, CI 1.11–1.28). Coagulase-negative staphylococci, *Escherichia coli* and *Pseudomonas aeruginosa* were the prevalent pathogens, though without difference between periods.

Conclusions: Rates of clinical NC, bacterial NC and bacterial growth percentage were not different between the study periods. Switching from IEO to SED had no effect on the NC rate.

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KEY WORDS: neonatal conjunctivitis (NC), newborn infant, erythromycin ointment, erythromycin drops, prophylaxis

Recommended prophylactic regimens for gonococcal neonatal conjunctivitis (NC) include: 1% silver nitrate solution, 1% tetracycline solution, 0.5% erythromycin solution, 2.5% povidone-iodine solution, and fusidic acid [1]. Silver nitrate is no longer available [2]. A shortage of individualized erythromycin ointment (IEO) in Israel led to a switch to shared erythromycin drops (SED) in our hospital (January 2014), i.e., from one ointment tube per neonate erythromycin ophthalmic ointment 0.5% (Fougera, Genmedix, Israel) to shared erythromycin 0.5% ophthalmic cream drops (Concept For Pharmacy Ltd., Israel). Questions emerged regarding cross-infection when using shared bottles.

*The first two authors contributed equally to this study

#For Morya Shnaider, this work fulfils part of the requirements for the MD degree at Rappaport Faculty of Medicine, Technion, Haifa, Israel

PATIENTS AND METHODS

This retrospective observational study was performed in the well-baby nursery at the Rambam Health Care Campus, Haifa, Israel. The institutional Helsinki Committee approved this study and waived the need for written informed consent.

STUDY POPULATION

The neonates (n=14,916) were divided into two study periods of 12 months each: IEO (1 January 2012 to 31 January 2013, n=9942) and SED (1 February 2014 to 31 January 2015, n=4974). Conjunctival swabs were obtained whenever eye discharge was noted.

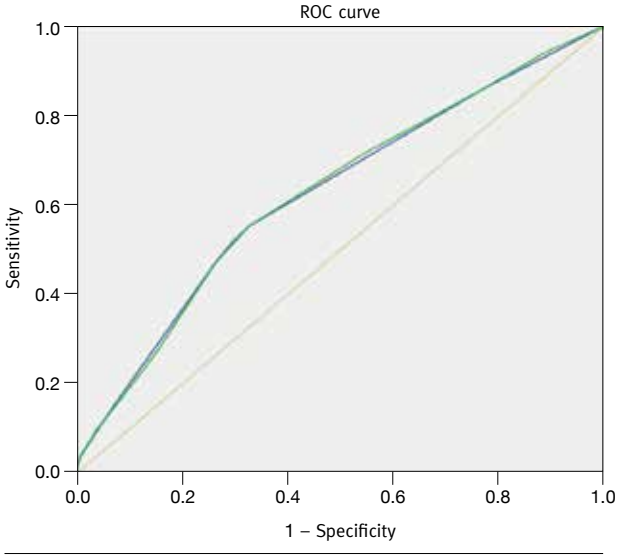
SAMPLING OF CONJUNCTIVAL SWABS AND DATA COLLECTION

Whenever a neonate had an eye exudate for 3 hours or more, a conjunctival swab was obtained for bacterial culture including medium for *Neisseria gonorrhoeae*. Diagnosis of *Chlamydia* in conjunctival swabs was not performed as it requires a special tissue culture or polymerase chain reaction. Furthermore, the typical incubation period for *Chlamydia trachomatis* conjunctivitis is 5 to 14 days after birth, which is too long considering the shorter length of stay (LOS) of our neonates (3–8 days).

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS (Statistics Products Solutions Services) 21.0 software for Windows. A P value < 0.05 was considered statistically significant. Chi-square test was used for comparison of differences between the two study periods regarding mode of delivery, gender, LOS, prolonged rupture of membranes, maternal intrapartum fever,

Figure 1. The area under the receiver operating characteristic (ROC) curve was used as a measure of model discrimination



and bacterial species growing in conjunctival swabs. Three NC parameters were compared between the IEO and SED periods: clinical NC rate, bacterial NC rate, and bacterial growth percentage. These were calculated as follows: clinical NC = number of conjunctival swabs/1000 neonates, bacterial NC = number of culture-positive samples/1000 neonates, and bacterial-growth percentage = number of culture-positive samples/100 samples. Bivariate logistic regression was used for calculation of the odds ratios (OR) with 95% confidence intervals (95%CI) and *P* values in univariate analyses. All variables with a *P* value ≤ 0.1 in the univariate analysis were selected as candidates for the multivariable analysis model. Multivariable forward logistic regression analysis was performed to identify variables that were independently significantly associated with the rate of clinical conjunctivitis and with the rate of bacterial conjunctivitis. The area under the receiver operating characteristic (ROC) curve was used as a measure of model discrimination [Figure 1].

RESULTS

Compared to the IEO period, the SED period had more vaginally born neonates ($P = 0.016$) and significantly shorter LOS ($P \leq 0.001$). Univariate analyses showed that male gender (1.47-fold), cesarean delivery (2.09-fold), and longer LOS (2.31-fold) were significantly associated with greater clinical NC rates. Cesarean delivery and longer LOS were associated with increased bacterial NC rate by 1.66-fold and 2.81-fold, respectively.

A multivariable forward logistic regression analysis [Table 1] showed that male gender ($P < 0.001$, OR 1.48, 95%CI 1.21–1.81) and LOS ($P < 0.001$, OR 1.24, 95%CI 1.18–1.29) were independently significantly associated with clinical NC rate. Only LOS was independently significantly associated with bacterial NC rate ($P < 0.001$, OR 1.19, 95%CI 1.11–1.28). The study periods were not associated with either clinical NC rate (SED vs. IEO: 28.6 vs. 26.7/1000 neonates, $P = 0.55$) or bacterial NC rate (SED vs. IEO: 4.4 vs. 4.2/1000 neonates, $P = 0.56$). However, both rates were significantly associated with longer LOS, regardless of delivery mode.

To test whether the non-significant variable "study period" affected other variables in the regression model, "study period" was forced into the model via the "ENTER" method [Table 1]. This led to non-significant *P* values of 0.138 and 0.803 for clinical and bacterial NC, respectively, but with minimal change in the other variables of the model.

Table 1. Adjusted odds ratios for the number of **[A]** conjunctival samples and of **[B]** culture-positive samples/1000 neonates by perinatal and neonatal risk factors

[A] Conjunctival samples/1000 neonates

	Stepwise analysis (model with period)		Stepwise analysis (model without period)	
Variable	***P***	**Adjusted OR (95%CI)**	***P***	**Adjusted OR (95%CI)**
Gender Female Male	‹ 0.001	1.0 1.48 (1.21–1.81)	‹ 0.001	1.0 1.48 (1.21–1.81)
Study period 1 Jan 2013 to 31 Dec 2014 2 Feb 2014 to 1 Jan 2015	0.138	1.0 1.79 (0.951–1.437)		
Length of stay days)	‹ 0.001	1.23 (1.18–1.29)	‹ 0.001	1.24 (1.18–1.29)
AUC_{ROC}		0.635 (0.61–0.66)		0.64 (0.61–0.67)

[B] Culture-positive samples/1000 neonates

	Model (ENTER) with period		Stepwise analysis (model without period)	
Variable	***P***	**Adjusted OR (95%CI)**	***P***	**Adjusted OR (95%CI)**
Study period 1 Jan 2013 to 31 Dec 2014 2 Feb 2014 to 1 Jan 2015	0.803	1.0 1.07 (0.63–1.8)		
Length of stay (days)	‹ 0.001	1.19 (1.11–1.28)	‹ 0.001	1.19 (1.11–1.28)
AUC_{ROC}		0.629 (0.6–0.66)		0.624 (0.6–0.65)

AUC_{ROC} = area under curve receiver operating characteristic, OR = odds ratio, CI = confidence interval

DISCUSSION

The shortage of a particular antimicrobial agent is an important reason for rapid and forced changes of treatment/prevention policies, and this is noteworthy even on the general level. In this regard, the use of shared eye drops has the potential of cross-infection. Our study aimed to show that local erythromycin prophylaxis for neonatal ophthalmia is safe even if administered from shared bottles.

Erythromycin prophylaxis reportedly has no effect on chlamydial conjunctivitis [2,3]. Hence, on behalf of the Canadian Pediatric Society, Moore et al. [2] recommended discontinuing this practice. Screening and treatment of pregnant women for *Chlamydia* in 1993 led to a dramatic decrease of perinatal chlamydial infections in the U.S., according to the Centers for Disease Control and Prevention 2010 [2-4]. Even though local erythromycin prophylaxis is still being used in some units, many delivery units in developed countries have stopped the routine prophylaxis due to the lack of proven efficacy against chlamydial infection, which today is the main causative agent for neonatal ophthalmia requiring antimicrobial treatment.

Our results show that using erythromycin drops from a shared bottle does not increase the bacterial NC rate. This might be the attributed to the high awareness of nurses regarding cross-infection, meticulous hand washing, and avoiding contact between opening of the erythromycin bottle and the neonate's eyes. Haas et al. [5] reported that bacteria grew in only 15.6% of swabs, mainly coagulase-negative *Staphylococcus*, *Staphylococcus aureus* and *Klebsiella* spp, while ours included coagulase-negative *Staphylococcus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, though without significant difference between periods.

Our study did have some limitations, namely, eye discharge was sampled only from hospitalized neonates, and conjunctival swabs were not tested for *Chlamydia*.

In conclusion, switching from erythromycin ointment to drops did not increase the rate of neonatal bacterial conjunctivitis.

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