Prophylaxis of Ophthalmia neonatorum – A nationwide survey of the current practice in Austria

Ojan Assadian¹, Afshin Assadian³, Christoph Aspöck¹, Daniela Hahn¹, and Walter Koller¹
¹Division of Hospital Hygiene, Institute of Hygiene of the University of Vienna Medical School, and
²Department of Gynaecology & Obstetrics, Wilhelminenspital, Vienna, Austria

Prophylaxe der Ophthalmia neonatorum – Spektrum der eingesetzten Substanzen und aktuelle Handhabung in Österreich


Ergebnis: Insgesamt kommen in Österreich 7 Substanzen mit folgender Häufigkeit zur Anwendung: Erythromycin 41,8%; Gentamicin 21,3%; Silbernitrat 18,7%; Tetracyclin 9%; PVP-Jod 4,9%; Neomyzin 2,5%; Chloramphenicol 1,1%.

Schlussfolgerung: Wir beobachten ein heterogenes Spektrum von sieben Substanzen zur Prophylaxe. Darunter wurden zwei Antiseptika und fünf Antibiotika angegeben. 71% der Anwender setzen dabei Substanzen ein, die auch in internationalen Empfehlungen für diese Indikation genannt werden (Erythromycin, Silbernitrat und Tetracyclin).

83,5% der Krankenhäuser Österreichs wollen ihr derzeit eingesetztes Regime nicht ändern, solange es keine einheitliche österreichweit gültige Richtlinie gibt, obwohl 43,6% von ihnen regelmäßig eine chemisch induzierte Konjunktivitis bei Neugeborenen beobachten.

Schlüsselwörter: Ophthalmia neonatorum, Credé’s prophylaxis, neonatal conjunctivitis, antibiotic prophylaxis, chemical conjunctivitis, bacterial conjunctivitis, questionnaire, prophylactic agents.

Introduction
In 1881 the gynecologist Carl Sigmund Franz Credé (1819-1892) introduced the use of 2% Silver nitrate solution as a prophylactic agent against ophthalmia gonorrhoea neonatorum. After observation of frequent eye-irritations, this was changed to a 1% Silver nitrate solution. This change of regimen reduced the yearly incidence of neonatal conjunctivitis from 13.6% to 0.5% [1, 2]. Since 1928 Austrian law has regulated the routine use of Ophthalmia neonatorum prophylaxis. Austrian midwives have been obliged to execute the prophylaxis in two steps: First, mechanical cleansing of the eye-lids before the infant opens them for the first time and second, instillation of one 1% Silver nitrate drop into each conjunctival sac.

Due to the extended knowledge of other possible pathogens such as Chlamydia trachomatis, Staphylococci, gram-negative bacteria and viruses as well as the avail-
ability of different antimicrobial agents, the decree was modified in 1970. From then on midwives could either use 1% Silver nitrate or any substance recommended by the public health authorities for prophylaxis of Ophthalmia neonatorum. In 1990 Austrian health authorities recommended 1% Silver nitrate solution, 1% Tetracycline ointment, 0.5% Oxytetracycline-hydrochloride ointment with Polymyxin-B-sulfate or 1% Erythromycin ointment for prophylaxis [3]. The last change in the legal situation of Ophthalmia neonatorum prophylaxis took place in 1998. Midwives were now allowed to use prophylactic medication without a doctor’s prescription if the application of the substance used was in accordance with good medical practice in addition to being recommended by the public health authorities. However, the use of prophylaxis and the suitability of prophylactic agents have continued to be challenged during the last decade [4–6]. The aim of our nation-wide survey was to elicit the present situation and practice of Ophthalmia neonatorum prophylaxis for the first time after 71 years of use in Austria. Also, we wanted to know which substances were in use, the mode and timing of application and if any desire for an unequivocal guideline for the prevention of Ophthalmia neonatorum exists.

Methods

An anonymous questionnaire was sent to 107 hospitals with obstetric units and to all 490 registered community midwives in Austria, together looking after a yearly total of approximately 70,000 births. We inquired about the routine of Ophthalmia neonatorum prophylaxis and the agents used, the reason for selecting agents, details about the modalities of administration and the frequent observation of complications, particularly chemical conjunctivitis (e.g. postprophylactic eye irritation). Chemical conjunctivitis was defined as eye discharge lasting no longer than 24 hours after application of a prophylactic agent [7]. The total numbers of post prophylactic eye irritations were not enquired. We concentrated on the question, whether health professionals using Ophthalmia neonatorum prophylaxis observed adverse effects, and if so, to which substances. Analysis of the data was performed with SPSS 9.0 (SPSS Inc., Chicago, Ill.). Two-tailed p-values were calculated by applying Chi-square test or Fisher’s exact Test, where appropriate. Mantel-Haenszel weighted Odds ratio (OR) together with Cornfield 95% Confidence intervals (CI) were computed. 91.6% (98/107) of the Hospitals and 7.6% (37/490) of the community midwives returned the questionnaire. Of the 98 hospital-questionnaires, only 97 could be evaluated since one hospital had recently closed down the maternity-unit. Three of the questionnaires sent to community midwives returned with the postal remark “receiver unknown”, one midwife responded from Switzerland, where routine application of Credé’s prophylaxis was discontinued ten years ago. Thirty-three of the midwife-questionnaires were evaluated, making a total of 96.3% (130/135) evaluable questionnaires.

Results

Routine application of Ophthalmia neonatorum prophylaxis in Austria

Ophthalmia neonatorum prophylaxis is being routinely administered by 96.9% (94/97) of responding maternity units and by 84.9% (28/33) of responding community midwives. Two hospitals only applied prophylaxis after vaginal births or premature rupture of membranes. In one hospital, Ophthalmia neonatorum prophylaxis is only applied after informed consent of the parents regarding advantages and side effects. Five community midwives did not apply any prophylaxis unless the parents explicitly wished so.

Reasons behind the choice of prophylactic agent

In 28.7% (35/122), pediatricians determined the agent, 14.8% (18/122) were following recommendations according to previous governmental decrees, 12.3% (15/122) executed hospital policy. Good experience with the agent in the past determined the choice in 9.0% (11/122). 4.9% (6/122) chose the agent because of specific effectiveness against Chlamydia and gonococci and 4.1% (5/122) claimed effectiveness against Chlamydia infection to explain their decision. Hospital pharmacists determined the choice in 3.3% (4/122) and ophthalmologists in 2.5% (3/122). One answer was illegible, one claimed tradition to be the reason for applying the prophylactic agent and one argued with hygiene requirements. 18% (22/122) of the respondents gave no reason for the choice of agent.

Substances used for prophylaxis of Ophthalmia neonatorum in Austria

Seven different substances are used by hospitals and community midwives for prophylaxis of Ophthalmia neonatorum. Substances and their use are listed in detail in Table 1. Altogether, the three most commonly used sub-

<table>
<thead>
<tr>
<th>Substance</th>
<th>Hospitals</th>
<th>Community midwives</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>n %</td>
<td>n %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>51 41.8</td>
<td>38 40.4</td>
<td>13 46.4</td>
<td>0.78</td>
<td>0.31–2.01</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>26 21.3</td>
<td>20 21.3</td>
<td>6 21.4</td>
<td>0.99</td>
<td>0.33–3.40</td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>24 19.7</td>
<td>23 24.5</td>
<td>1 3.6</td>
<td>8.75</td>
<td>1.27–373.42</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>11 9.0</td>
<td>6 6.4</td>
<td>5 17.9</td>
<td>0.31</td>
<td>0.07–1.44</td>
</tr>
<tr>
<td>Povidone-Iodine</td>
<td>6 4.9</td>
<td>4 4.3</td>
<td>2 7.1</td>
<td>0.58</td>
<td>0.08–6.76</td>
</tr>
<tr>
<td>Neomycin</td>
<td>3 2.5</td>
<td>2 2.1</td>
<td>1 3.6</td>
<td>0.59</td>
<td>0.03–35.90</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1 0.8</td>
<td>1 1.1</td>
<td>0 0.0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
stances for Ophthalmia neonatorum prophylaxis in Austria are Erythromycin (41.8%; 51/122), Gentamicin (21.3%; 26/122) and Silver nitrate (19.7%; 24/122). Hospitals used, in decreasing order, Erythromycin, Silver nitrate and Gentamicin, whereas community midwives used Erythromycin, Gentamicin and Tetracycline.

**Observation of chemical conjunctivitis after the routine application of prophylactic agents**

43.6% (41/94) of the hospitals reported frequent observation of chemical conjunctivitis after the instillation of prophylactic agents as did fifty percent (14/28) of the community midwives. Details are shown in Table 2. Chemical conjunctivitis was observed most frequently with Silver nitrate (OR 4.95, 95% CI 1.67-16.42, p = 0.001), whereas Gentamicin was the best-tolerated substance (0.22, 95%CI 0.06-0.66, p = 0.003).

**Timing and mode of application of prophylaxis**

Asked about the timing of prophylaxis, 55.4% (72/130) answered that application occurs within 1 to 30 minutes after birth (64 Hospitals and 8 community midwives). 40.8% (53/130) stated that prophylaxis is applied between 30 minutes and 2 hours post partum (32 hospitals and 21 community midwives). One hospital and 4 midwives (3.8%; 5/130) did not comment on this question. 73.1% (95/130) stated that medication is simply instilled (72 hospitals and 23 community midwife). 23.1% (301/130) reported that they first cleaned the eyes of the newborn before the application of prophylactic agents as did fifty percent (14/28) of the community midwives. Details are shown in Table 2. Chemical conjunctivitis was observed most frequently with Silver nitrate (OR 4.95, 95% CI 1.67-16.42, p = 0.001), whereas Gentamicin was the best-tolerated substance (0.22, 95%CI 0.06-0.66, p = 0.003).

**Table 2. Observation of chemical conjunctivitis (CC) according to stratification, by hospitals and community midwives**

<table>
<thead>
<tr>
<th>Hospitals</th>
<th>CC pos.</th>
<th>CC neg.</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>18</td>
<td>20</td>
<td>1.29</td>
<td>0.69-2.41</td>
<td>0.55</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>3</td>
<td>17</td>
<td>0.17</td>
<td>0.03-0.66</td>
<td>0.004*</td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>17</td>
<td>6</td>
<td>5.55</td>
<td>1.76-19.15</td>
<td>0.0008*</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>2</td>
<td>4</td>
<td>0.63</td>
<td>0.05-4.67</td>
<td>0.63</td>
</tr>
<tr>
<td>PVP-Iodine</td>
<td>1</td>
<td>3</td>
<td>0.42</td>
<td>0.001-5.46</td>
<td>0.69</td>
</tr>
<tr>
<td>Neomycin</td>
<td>0</td>
<td>1</td>
<td>0.00</td>
<td>0.00-50.41</td>
<td>1.00</td>
</tr>
<tr>
<td>Chloramph.</td>
<td>0</td>
<td>1</td>
<td>0.00</td>
<td>0.00-50.41</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Total

<table>
<thead>
<tr>
<th>CC pos.</th>
<th>CC neg.</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>25</td>
<td>26</td>
<td>1.33</td>
<td>0.60-2.88</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5</td>
<td>11</td>
<td>0.22</td>
<td>0.06-0.66</td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>18</td>
<td>6</td>
<td>4.95</td>
<td>1.67-16.42</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>4</td>
<td>7</td>
<td>0.67</td>
<td>0.14-2.83</td>
</tr>
<tr>
<td>PVP-Iodine</td>
<td>2</td>
<td>4</td>
<td>0.59</td>
<td>0.05-4.35</td>
</tr>
<tr>
<td>Neomycin</td>
<td>1</td>
<td>2</td>
<td>0.60</td>
<td>0.01-11.90</td>
</tr>
<tr>
<td>Chloramph.</td>
<td>0</td>
<td>1</td>
<td>0.00</td>
<td>0.00-47.51</td>
</tr>
</tbody>
</table>

*Significant difference in observation of chemical conjunctivitis

**Desire for change of the current practice:**

(only hospitals with routine application included)

43.6% (41/94) of hospitals stated, that they do not wish to change their current practice, unless unequivocal nation-wide guidelines are released.

**Discussion**

Even after 115 years of use, Ophthalmia neonatorum prophylaxis is not obsolete and an important issue in maintaining public health. Countries having discontinued the practice of Ophthalmia neonatorum prophylaxis like Sweden and Denmark experience a rise in the incidence of Ophthalmia neonatorum due to gonococci [8, 9]. Interestingly, although prophylaxis is not administered routinely in the UK a decreasing incidence of Ophthalmia neonatorum has been reported. On the other hand, in the USA and Canada a rise in the incidence of Ophthalmia neonatorum has been observed, even though the respective health authorities recommend prophylaxis of Ophthalmia neonatorum. Austrian authorities believe in prophylaxis, since prevention, especially in pediatric patients, is preferable to treatment of a manifest disease. The German-Austrian Society for Perinatal Medicine also recommends the further use of Ophthalmia neonatorum prophylaxis [10].

The onset of Ophthalmia neonatorum symptoms usually develops days after discharge from hospital. It depends on the causative pathogen and ranges from 2 up to 14 days post partum. Conjunctivitis presenting after 2 to 4 days post partum is usually due to an infection caused by *Neisseria gonorrhoeae*, after 5 to 7 days due to *Herpes simplex virus* and after 5 to 14 days due to *Chlamydia trachomatis* [11].

The most severe form of Ophthalmia neonatorum is caused by *Neisseria gonorrhoeae*. It may result in blind-
ness by penetration of the cornea in a very short time. Gonococcal Ophthalmia neonatorum has a dramatic clinical presentation, though it is a treatable condition when diagnosed promptly. Presently, the incidence of gonococcal infections is falling in many industrialized countries. Nevertheless, an increase of non-gonococcal Ophthalmia neonatorum can be observed with an incidence of up to 22% in industrial countries [12].

According to the Centers for Disease Control and Prevention, the most commonly isolated pathogen causing Ophthalmia neonatorum is *Chlamydia trachomatis*. It induces a symptomatic conjunctivitis after five to fourteen days post partum. At that time, most newborns and their mothers are already discharged from hospital care and are no longer under close medical observation. *Chlamydia trachomatis* may impair vision as a result of corneal and conjunctival scarring, vascularisation [13] and formation of pseudo-membranes [14]. However, this complication results only, if the patient is frequently re-infected [15-17], which usually does not occur in industrialized countries. Therefore, this clinical presentation is most commonly seen in developing countries. Without recurrent infections with *Chlamydia trachomatis*, the symptoms subside within one to three weeks, making chlamydial Ophthalmia neonatorum a usually self-limiting infection.

Other pathogens, less frequently causing Ophthalmia neonatorum are Staphylococci, Streptococci, Pseudomonad, other gram-negative organisms and Herpes viruses. The latter are not as frequently observed as are gonococci or chlamydia, and most of them do not lead to severe complications.

**Properties of an ideal substance for Ophthalmia neonatorum prophylaxis**

The ideal substance for Ophthalmia neonatorum prophylaxis should be active against all relevant bacterial and viral pathogens. To avoid a decrease of bonding in the first days of life, it should not induce chemical conjunctivitis. Additionally, the substance should be inexpensive. Bacterial contamination of eye drop bottles ranges from 12.9% to 27% [18, 19], showing significant differences between in-hospital and outpatient use. Hence, to avoid potential cross-infections by contaminated eye drop bottles or ointment vehicle [20], disposable containers should be used.

**International guidelines and recommended Substances**

Our study revealed a variety of substances and practices used for prophylaxis against Ophthalmia neonatorum in Austria. In 1990, Austrian health authorities recommended the use of Silver nitrate, Erythromycin, Tetracycline or Oxytetracycline-hydrochlorid ointment in combination with Polymyxin-B-Sulfate for the mandatory prophylaxis against Ophthalmia neonatorum. In 1998, the CDC recommended the use of Silver nitrate, Erythromycin or Tetracycline [21]. Other substances mentioned as prophylactic agents were Bacitracin and Povidone-Iodine. The Canadian STD Guidelines of 1992 [22] did recommend the use of Silver nitrate, Erythromycin or Tetracycline. In the 1998 Canadian STD Guidelines [23], other pathogens causing Ophthalmia neonatorum like Herpes simplex virus and *Staphylococcus aureus* were mentioned. In these guidelines it was stated, that none of the above substances cover the whole spectrum of possible causative pathogens.

In the UK, the North Thames (East) Regional Audit does not recommend the use of prophylaxis against Ophthalmia neonatorum, and no prophylaxis is suggested because of the following reasons: ocular prophylaxis with Silver nitrate, Erythromycin or Tetracycline eye ointment mask parental infection. Extra-ocular sites are not treated and prophylactic substances are not necessarily effective in preventing both gonococcal and chlamydial Ophthalmia neonatorum [24]. Furthermore, facilities for early diagnosis and management are available.

The foundation of the above guidelines is the fact, that Ophthalmia neonatorum is still a health issue. However, there has been a shift in the spectrum of the causative pathogens. As the CDC and the Canadian STD Guidelines explicitly mention, the prevalence of chlamydial infection is on the rise, whereas the numbers of gonococcal infections are falling. However, Silver nitrate is highly active against *Neisseria gonorrhoeae* but much less effective against *Chlamydia trachomatis* and viruses [25-27]. It is also the substance with the highest potential for chemical conjunctivitis. In our survey, 75% of the respondents using Silver nitrate observed chemical conjunctivitis. If not applied in single use containers, the solvent will evaporate with time increasing the concentration of Silver nitrate. This will lead to higher numbers of eye irritations. To our knowledge, there are no reports of resistance of *Neisseria gonorrhoeae* to Silver nitrate. Tetracycline is active against *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. It also covers Streptococci, *Haemophilus influenzae*, Pseudomonas spp. and Staphylococci. However, resistances are reported [28-30], making this substance no longer a suitable first line agent for the empirical prevention of Ophthalmia neonatorum. 36% of the respondents using Tetracycline observed chemical conjunctivitis. Erythromycin is highly potent against *Chlamydia trachomatis*, but less effective against gonococci than Tetracycline or Silver nitrate. In our survey, it was reported to less frequently cause chemical conjunctivitis (49% vs. 75%) than Silver nitrate but more frequently than Tetracycline (49% vs. 36%). It is expensive and ineffective against viruses. Finally, the use of antimicrobial substances like Erythromycin and Tetracycline cannot prevent conjunctival infection with pathogens resistant to these substances [31, 32]. Each of the above named substances fulfill only some aspects of the desired profile for an ideal agent for prophylaxis against Ophthalmia neonatorum and no single topical agent is effective to ideally prevent ocular complications of both *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

Even though only briefly mentioned in the CDC Guideline, Povidone-Iodine has advantages compared to Erythromycin, Tetracycline and Silver nitrate. It has a broader antimicrobial spectrum as well as effectiveness against viruses including herpes simplex virus II [33]. Besides its antibacterial and antiviral capacity, there are no reports of resistance, which is explained by the chemical mechanism of action due to oxidizing effects of free
iodine on functional groups of amino acids, nucleotides and the double bonds of unsaturated fatty acids [34]. Additionally, it turns the surface of the eye brown for a few minutes. This feature can be used as a control of proper application into the eye of the newborn.

Good clinical results were published with Povidone-Iodine at a concentration of 2.5% [25]. However, the issue of concentrations still needs to be evaluated in further clinical trials, since newest in vitro studies suggest that 1.25% Povidone-Iodine is a sufficient concentration for this indication [35]. To avoid potential transmission of infection via contamination of the container, we recommend a disposable container, containing 0.5 ml of 2.5% Povidone-Iodine. In October 2000, a national consensus meeting under participation of pediatricians, gynecologists, ophthalmologists and clinical microbiologists was held. It was agreed that after cleaning the newborns eyelids mechanically, prophylaxis of Ophthalmia neonatorum should be carried out using 2.5% Povidone-Iodine taken from a disposable sterile container. The result of this consensus meeting was accepted by Austrian health authorities [36] in November 2000.

Conclusion

Seven different substances are used in Austria for prophylaxis against Ophthalmia neonatorum. 70.5% (86/122) of the routine applicants are using substances recommended in international guidelines (Erythromycin, Silver nitrate and Tetracycline). Thirty hospitals and midwives (24.6%) are using Gentamicin, Neomycin or Chloramphenicol, substances for which no evidence based efficacy for prophylaxis of Ophthalmia neonatorum has been demonstrated through clinical trials. Povidone-Iodine is used by 4.9% (6/122). In our opinion, it is the most favorable of all recommended agents. It has the broadest antibacterial spectrum as well as viricidal capacities. Unlike antibiotics, bacterial resistance has not been reported. 83.5% of our maternity units do not want changes in their current routine, unless there is a nation-wide agreement for Ophthalmia neonatorum prophylaxis, even though 43.6% of all hospitals report frequent observation of chemical conjunctivitis.

References


Correspondence: Ojan Assadian, M.D., DTM & H, Institute of Hygiene of the University of Vienna Medical School, Division of Hospital Hygiene, University Hospital Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria, E-mail: ojan.assadian@akh-wien.ac.at

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Neue Aspekte zur Prophylaxe der Ophtalmia neonatorum (Credé prophylaxis)

Nach derzeitigem Stand der Wissenschaft ist PVP-Jod 1,25% als isoosmolarische Lösung das Antiseptikum der Wahl für die Credésche Prophylaxe. PVP-Jod ist die beste Alternative zu Silbernitrat, weil es ein breites Keimspektrum abdeckt und besser verträglich ist.

Empfohlene Rezeptur:

- Povidone iodine (Low molecular with a K-value of <18) 0.125 g
- sodium chloride 0.08 g
- disodium hydrogen phosphate X 12 H₂O0.025 g
- water for injection ad 10 g