Aminoglycosides were associated with higher rates of surgical patent ductus arteriosus closure in preterm infants

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**Abstract**

**Aim:** In animal studies, aminoglycosides induced ductus arteriosus relaxation in a dose-dependent fashion. We tested the hypothesis that antibiotic treatment of preterm infants with aminoglycosides is associated with higher rates of surgical patent ductus arteriosus (PDA) closure.

**Methods:** Preterm infants (birthweight <1000 grams or gestational age <29 weeks) enrolled in 62 German neonatal intensive care units (NICUs) were analysed. NICUs were stratified according to the use of aminoglycosides as first-line antibiotics.

**Results:** Baseline data were not different when NICUs using aminoglycosides (n = 9965 infants) were compared to NICUs using other antibiotics (n = 1948 infants). Rates of surgical PDA closure were 5.9% for NICUs using aminoglycosides; 6.2% for units using gentamicin; and 5.0% for NICUs using tobramycin compared to 4.1% in NICUs using other antibiotics (P <.001, P <.001 and P =.140, respectively, Fisher's exact test). Indomethacin and ibuprofen use was more common in NICUs using aminoglycosides (41% vs 33%, P <.001, Fisher's exact test). Gentamicin trough levels were higher in NICUs with surgical closure rates above the mean (median 2.0 µg/mL, inter-quartile range 0.8-4.0 µg/mL vs 1.2 µg/mL, IQR 0.8-1.7, P <.001, Mann-Whitney U test).

**Conclusion:** First-line antibiotic treatment of preterm infants with aminoglycosides was associated with higher rates of surgical PDA closure.

**Keywords**

aminoglycosides, extremely preterm infants, patent ductus arteriosus, surgical ligation
INTRODUCTION

Patent ductus arteriosus (PDA) affects about 32%-60% of extremely preterm infants born at 22-28 weeks of gestation. An imbalance of vasodilatory stimuli, a lack of contractile mechanisms and the immaturity to react to regular postnatal PDA closure stimuli can lead to a delayed or absent closure of the ductus arteriosus.

There are multiple known risk factors for PDA: early gestational age, low birthweight, respiratory distress syndrome, sepsis, exposure to antenatal nonsteroidal anti-inflammatory drugs (NSAID), intubation, lack of antenatal steroids or maternal diabetes. Other potential risk factors, such as small for gestational age (SGA), sex, genetic susceptibility, maternal drugs and various, frequently used drugs in NICUs, such as furosemide and aminoglycosides are being discussed controversially. If PDA closure does not occur spontaneously, common treatment methods are pharmacological treatment with NSAID, that is indomethacin and ibuprofen and surgical ligation.

Gentamicin and tobramycin are aminoglycoside antibiotics, which are frequently used in preterm infants who are at high risk for sepsis. Aminoglycosides are mainly used for the treatment of suspected or proven early onset sepsis. There are various treatment and dosing guidelines leading to an inconsistent and centre-specific use of aminoglycosides. Regarding a possible association with aminoglycoside use, different studies found dose-dependent vasodilatory effects of aminoglycosides on the ductus arteriosus of mice and rats. Vucovich et al found increased PDA rates in aminoglycoside-treated infants born 23-25 and 32-38 weeks of gestation, but not in infants born 26-31 weeks of gestation.

Alternative antibiotics which are used to treat or prevent early onset sepsis include ampicillin and cefotaxime. However, Clark et al. found a higher mortality rate in infants, treated with ampicillin and cefotaxime compared to infants treated with ampicillin and gentamicin.

Most NICUs in Germany are using a combination of ampicillin and aminoglycosides as first-line antibiotic treatment. We analysed centre-specific antibiotic treatment standards and their association with surgical PDA closure in a large cohort of preterm infants.

METHODS

The German Neonatal Network (GNN) is a prospective population-based multicentre cohort study. Infants with a birthweight <1500 g and a gestational age <37 weeks were enrolled in 62 level III NICUs in Germany. For this observational study, we included infants with a gestational age 22 ± 0 to 28 ± 6 weeks or a birthweight <1000 grams. All infants were born and discharged from hospital between January 2009 and December 2018. We excluded infants with incomplete data sets regarding aminoglycoside use and PDA therapy. Written informed consent was given by all parents of participating infants. The GNN study was approved by the ethics committee at the University of Lübeck and at each participating study centre.

All data of the GNN were recorded primary on case report forms by the attending neonatologist. After monitoring by means of on-site visits of a physician or study nurse, all data were entered into the central database. The data for this study were taken from the GNN database, including basic data on aminoglycoside use, PDA therapies such as indomethacin or ibuprofen use, surgical ligation and steroid use.

We determined the three most frequently used antibiotics for each participating NICU and split the study centres into two groups according to their overall antibiotic use: NICUs with aminoglycosides within the top three antibiotics as first group and NICUs without aminoglycosides within the top three antibiotics as second group. The infants were analysed in two groups according to the NICU they were admitted to.

In a subset of eight NICUs, data were available on cumulative aminoglycoside doses and treatment days of 552 infants. These infants were born between January 2009 and June 2014. All eight centres used aminoglycosides as first-line antibiotic; the infants were all as well treated with vancomycin. Within this group, we assessed 272 infants with data on gentamicin trough levels. In twelve infants, trough levels were below the centre-specific limit of quantification. In these cases, we divided each lower limit of quantification by two and added the data to our analysis.

Statistical methods

Data were analysed using SPSS, version 25.0 (IMC Corp, New York, USA). Baseline data were given as median and inter-quartile range (IQR) or percentage and compared with Mann-Whitney U and Fisher’s exact test. For comparison of PDA-treatment rates, we used Fisher’s exact test. Data of gentamicin trough levels were given as median and IQR; for comparison, we used Mann-Whitney U test. We performed a multivariable logistic regression model containing known risk factors for PDA: gestational age, oxygen need in the first 12 hours as a measure for respiratory distress
3 | RESULTS

We included 11 913 infants with complete data sets from 62 study centres. There were 53 NICUs using aminoglycosides as first-line antibiotics (n = 9965 infants, 83.6%, first group) and 9 NICUs using other than aminoglycosides as first-line antibiotics (n = 1948 infants, 16.4%, second group). Among the first group, gentamicin was used in 41, tobramycin in 12 NICUs. The 9 NICUs using other than aminoglycosides as first-line antibiotics were university hospitals in 7/9 cases. There were no differences in the number of infants included. The NICUs were not from a particular region.

Baseline data are given in Table 1. Median gestational age in the aminoglycoside group was 27 weeks (IQR 25.4-28.3) and median birthweight 860 grams (IQR 680-990) and did not differ between the two groups. With regard to sex, multiple birth, SGA and antenatal steroids, there were no differences between the groups. Sepsis rates and mortality rates due to sepsis were not different between groups. The total mortality rate was lower (P < .001, Fisher’s exact test) in the low-aminoglycoside group (Table 1).

With respect to the treatment rates in both groups, 6089/9965 (61.1%) received gentamicin and 2166/9965 (21.7%) tobramycin in the aminoglycoside group. Regarding 125/9965 infants (1.3%), who received both tobramycin and gentamicin, and the result showed a total of 8130/9965 (81.6%) of infants receiving aminoglycoside treatment in the first group. In the low-aminoglycoside group (second group), 432/1948 (22.3%) received aminoglycosides, among them 427/1948 (21.9%) gentamicin, 7/1948 (0.4%) tobramycin and 2/1948 (0.1%) both gentamicin and tobramycin.

In our cohort, 667/11913 (5.6%) underwent surgical PDA closure. In the aminoglycoside group, 558/9965 (5.6%) needed surgical closure, whereas in the low-aminoglycoside group only 79/1948 (4.1%) had surgical PDA closure (P = .001, Fisher’s exact test), see Table 2. The postnatal day of surgical PDA closure did not differ between the groups (P = .314, Mann-Whitney U test). Ibuoprofen and indomethacin use was higher in the aminoglycoside group (41.1% vs 32.7%, P < .001); the use of steroid hormones and hydrocortisone was higher in the low-aminoglycoside group (21.8% vs 33.4%, P < .001 and 16.1% vs 27.3%, P < .001, respectively).

In the aminoglycoside group, the rate of surgical PDA closure was significantly higher (6.2%, 474/7695) in centres with gentamicin use (n = 41) when compared to the low-aminoglycoside group (4.1%, 79/1948; P < .001, Fisher’s exact test). There was no significant difference in the group of tobramycin use (n = 12 NICUs) with surgical PDA closure in 5.0% (114/2270) and the low-aminoglycoside group (4.1%, P = .134, Fisher’s exact test, Figure 1).

In order to evaluate cumulative doses and serum trough levels, we used available data from eight NICUs using gentamicin as first-line antibiotic. Infants in three NICUs, which had rates of surgical PDA closure above the mean rate of the cohort (≥5.6%), had higher gentamicin trough levels when compared to gentamicin trough levels in five NICUs with rates of surgical PDA closure below 5.6% (median 2.0 µg/mL, IQR 0.8-4.0 µg/mL vs median 1.2 µg/mL, IQR 0.8-1.7 µg/mL, P < .001, Mann-Whitney U test). There were also slightly more gentamicin treatment days in the group with higher rates of surgical PDA closure (median 4.5, IQR 3-7 vs median 4.0, IQR 3-5, P < .001). The cumulative doses of gentamicin did not differ between the two groups (P = .903, Mann-Whitney U test) (Table 3).

In a multiple logistic regression model, gentamicin treatment and tobramycin treatment were both associated with surgical PDA closure: OR 1.6 (95% CI 1.3-2.0, P < .001) and OR 1.3 (95% CI 1.1-1.8, P = .003), respectively. Moreover, gestational age, sepsis, oxygen use >40% in the first 12 hours of life, dobutamine and furosemide were associated with surgical PDA closure, whereas female gender, SGA and lack of antenatal steroids were not associated (Table 4).

**TABLE 1** Baseline data, sepsis and mortality

|                        | Group 1   | Group 2   |
|------------------------|-----------|-----------|
| **Aminoglycosides as** |           |           |
| **first-line antibiotics** | n = 9965 | n = 1948 |
| **Gestational age [weeks]** | 27 (25.4-28.3) | 26.9 (25.4-28.1) |
| **Birthweight [grams]** | 860 (680-990) | 860 (690-990) |
| **Gender [female]** | 4755 (47.7) | 927 (47.6) |
| **Multiple birth** | 3164 (31.8) | 604 (31.0) |
| **Small for gestational age** | 1738 (17.4) | 314 (16.1) |
| **Antenatal steroids** | 9144 (91.8) | 1892 (92.0) |
| **Sepsis** | 1591 (16.0) | 335 (17.2) |
| **Sepsis with candida** | 55 (0.6) | 5 (0.3) |
| **Death from sepsis** | 107 (1.1) | 15 (0.8) |
| **Overall mortality** | 596 (6.0) | 67 (3.4) |

Note: Data are given as median (IQR) or n (%).

*P < .001, Fisher’s exact test.
DISCUSSION

In our cohort, treatment in a NICU with aminoglycosides as first-line antibiotic was associated with higher rates of surgical PDA closure. Nevertheless, in the group of NICUs using aminoglycosides as first-line antibiotic, the rates of surgical PDA closure varied greatly, suggesting other than aminoglycoside-associated factors to influence the rate of surgical PDA closure. In a multiple logistic regression model, we found both gentamicin and tobramycin to be associated with surgical PDA closure. Previously reported risk factors for the need of surgical PDA closure like gestational age, severe respiratory distress syndrome, sepsis, furosemide and dobutamine treatment were associated with surgical PDA closure, whereas sex, SGA and lack of antenatal steroids were not associated in our cohort. A haemodynamically relevant PDA or a delay in the closure of PDA may lead to an increased morbidity and mortality.11-13 While spontaneous closure of the patent ductus arteriosus is reported in 16%-58% of VLBW infants,14-16 pharmacological or surgical treatment is often carried out.4 Prevalence data and treatment rates in other studies vary: Thompson et al found a PDA-treatment rate of 15% in a cohort of more than 43 000 VLBW infants. Vucovich et al found 8.3% of infants to have a symptomatic PDA in a huge multicentre NICU.
In the groups of infants born 23-25, 32-34, 35-37 and >38 weeks of gestation, aminoglycoside treatment was associated with higher PDA rates. However, in the groups of gestational age 26-28 and 29-31, there were no significant differences. A study by Mirea et al. found PDA in 25% of preterm infants <32 weeks of gestation. Spontaneous closure was achieved in 16% of infants, whereas 57% received indomethacin, 9% surgical ligation and 18% both pharmacological and surgical treatment. Aygün et al. found PDA to be closed spontaneously in 70% in a cohort of 422 VLBW infants with PDA. Ibuprofen was administered to 19.4%; 5.7% received surgical ligation and 5% both ibuprofen and surgical closure. Stoll et al. found treatment rates of 12%-50% of surgical ligation and 67%-82% indomethacin therapy in a multicentre cohort of extremely preterm infants 22-28 weeks of gestation among the infants presenting with PDA. Therapy was most common in the extremely preterm infants. In our multicentre cohort of extremely preterm infants, 39.7% of infants were treated pharmacologically for PDA and 5.6% by surgical ligation.

Overall, multicentre studies have reported a great variation in PDA-treatment rates among NICUs. The effects of PDA treatment on long-term morbidity and mortality are being discussed controversially, which may partly explain the variation in treatment rates among NICUs worldwide.

Hydrocortisone is often given to VLBW infants in the first days of life for prevention of bronchopulmonary dysplasia and inflammatory lung disease. It has an anti-inflammatory effect and thus may influence the ductus arteriosus by inhibiting the release of arachnoid acids and prostaglandin synthesis. In a randomised controlled trial, low-dose hydrocortisone was associated with lower rates of surgical PDA closure. A meta-analysis found early hydrocortisone to significantly reduce PDA treatment but also to be associated with an increased risk of gastrointestinal perforation if both hydrocortisone and NSAID were administered for PDA treatment. The differences in the use of hydrocortisone in both groups of our cohort might be explained by centre-specific protocols. In our low-aminoglycoside group, ibuprofen and indomethacin use was significantly lower than in the aminoglycoside group confirming the association with low rates of surgical PDA closure.

Our study shows that the majority of NICUs in Germany (53/62) use aminoglycosides as first-line antibiotic. Data on aminoglycoside effects on PDA, especially clinical data, are still scarce. Despite the fact that, in our cohort, centre-specific use of gentamicin was associated with higher rates of surgical PDA closure, and centre-specific first-line tobramycin use was not associated significantly. Vucovich et al found dose-dependent effects of aminoglycosides on in vivo and ex vivo ductus arteriosus of mice. Tobramycin had the most potent effect in preterm mice, whereas gentamicin had more effects on the ductus of term mice. Pre-treatment with indomethacin did not influence the gentamicin effects significantly.

Reese et al found dose-dependent vasodilatory effects of aminoglycosides on the ex vivo ductus arteriosus of mice. However, aminoglycoside doses used in the studies were much higher than those used in NICUs. A study by Kishibuchi et al found dose-dependent effects of gentamicin on the ductus arteriosus of rats in high doses. Standard doses of gentamicin did not have a prolonging effect on the ductus.

### Table 4: Multivariable logistic regression on risk factors of surgical closure for PDA

| Exposure                  | Exposed n (%) | PDA surgery n (%) | Univariate OR (95% CI) | Multivariable OR (95% CI) | P     |
|---------------------------|---------------|-------------------|------------------------|---------------------------|-------|
| Gender [female]            | 5682          | 316 (5.6)         | 1.0 (0.8-1.2)          | 1.1 (0.9-1.3)             | .255  |
| Gestational age [weeks]    | 11 913        | n.a.              | n.a.                   | 0.7 (0.7-0.7)             | <.001 |
| SGA [P < 10]              | 2052          | 144 (7.0)         | 1.3 (1.1-1.6)          | 1.2 (0.9-1.4)             | .129  |
| No antenatal steroids      | 977           | 80 (8.2)          | 1.6 (1.2-2.0)          | 1.2 (0.9-1.6)             | .117  |
| Postnatal oxygen 40%-59%   | 2940          | 186 (6.3)         | n.a.                   | 1.3 (1.0-1.6)             | .018  |
| Postnatal oxygen 60%-100%  | 2615          | 213 (8.1)         | n.a.                   | 1.3 (1.0-1.5)             | .025  |
| Sepsis                    | 1926          | 195 (10.1)        | 2.3 (1.9-2.7)          | 1.3 (1.1-1.6)             | .003  |
| Gentamicin                | 6516          | 426 (6.5)         | 1.5 (1.3-1.8)          | 1.6 (1.3-2.0)             | <.001 |
| Tobramycin                | 2173          | 150 (6.9)         | 1.2 (1.1-1.6)          | 1.3 (1.1-1.8)             | .003  |
| Furosemide                | 3627          | 417 (11.5)        | 4.2 (3.6-4.9)          | 2.5 (2.1-2.9)             | <.001 |
| Dobutamine                | 1718          | 197 (11.5)        | 2.7 (2.3-3.2)          | 1.4 (1.1-1.7)             | .002  |

Abbreviations: CI, confidence interval; n.a., not applicable; OR, odds ratio; PDA, patent ductus arteriosus; SGA, small for gestational age.
Valitalo et al demonstrated that the currently available dosing guidelines for aminoglycosides differ widely and often lead to inadequate or high trough levels in neonates. In our study, we found higher trough levels and treatment days of gentamicin in those NICUs with a higher rate of surgical PDA closure (≥5.6%). However, there were no differences in the gentamicin cumulative doses. Regarding morbidity, Aygün et al demonstrated a high rate of acute kidney injuries in patients with PDA (>50%), especially in those infants with both medical and surgical treatment of PDA. Acute kidney injury was associated with gentamicin use and birth-weight. PDA may impair the kidney perfusion and thus lead to a decreased clearance of aminoglycosides, aminoglycosides themselves are supposed to be nephrotoxic, and nonsteroidal anti-inflammatory drugs may further increase the nephrotoxic risk by decreasing renal perfusion.

In our cohort, we did not find a higher mortality in infants treated with ampicillin and cefotaxime, which Clark et al found in a cohort of 128,914 neonates admitted to a NICU. On the contrary, we found a lower mortality in those NICUs, which used other than aminoglycosides as first-line antibiotics. We attribute this finding to centre-specific low mortality.

Our study had several limitations. The observational study design is an important limitation as NICUs using aminoglycosides might have higher rates of surgical PDA closure for other reasons than aminoglycoside use. Data were analysed according to the general antibiotic policy of the NICUs, and infants were analysed according to the NICU they were admitted to. Data on cumulative doses and treatment days were only available on infants treated in a subset of NICUs using aminoglycosides as first-line treatment. There were no standard dosing protocols among the centres. Thus, we could not analyse further details regarding the differences in the results of trough levels and cumulative doses or regarding the differences of gentamicin and tobramycin effects on PDA.

Strengths of our study design were the large number of patients and NICUs and the very consistent results, including high rates of surgical PDA closure but also high rates of treatment with indomethacin or ibuprofen in NICUs using aminoglycosides as first-line antibiotics. The higher survival rate in the low-aminoglycoside group might induce survival of extremely premature infants who have a higher rate of surgical PDA closure. This may support our findings.

5 | CONCLUSION

In our large cohort study, aminoglycoside treatment was associated with higher rates of surgical PDA closure in extremely preterm infants. In a subset analysis, infants in NICUs with a higher rate of surgical closure (≥5.6%) had higher gentamicin trough levels. In the vulnerable cohort of extremely preterm children, neonatologists should be aware of the potential side effects of aminoglycosides and the possible association with PDA. Trough level thresholds should be checked carefully; adjustments of doses or intervals should be undertaken if needed. Further prospective studies are required to better understand the effects of frequently used drugs in NICUs on PDA in extremely preterm infants.

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CONFLICTS OF INTEREST

The authors have no potential conflicts of interest to disclose.

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