An optimised versus standard dosing regimen of vancomycin in infants with Gram-positive sepsis (NeoVanc): a multi-centre randomised, open-label, phase IIb, non-inferiority trial

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Summary

Background Vancomycin is the most widely used antibiotic for neonatal Gram-positive sepsis, but clinical outcome data of dosing strategies are lacking. The NeoVanc programme comprised extensive pre-clinical studies to inform an optimised vancomycin dosing randomised controlled trial (RCT). The primary objective was to compare the efficacy of an optimised regimen to a standard regimen in infants with late onset sepsis, known or suspected to be caused by Gram-positive microorganisms.

Methods NeoVanc was an open-label, parallel, phase IIb, non-inferiority RCT comparing efficacy and toxicity of an "optimised" regimen of vancomycin to a "standard" regimen in infants ≤90 days. Infants with ≥3 clinical/laboratory sepsis criteria or confirmed Gram-positive sepsis with ≥1 clinical/laboratory criterion were enrolled from 22 neonatal intensive care units in 5 European countries. Randomisation was 1:1 to the optimised regimen (25mg/kg loading dose followed by 5±1 days of 15 mg/kg q12h or q8h dependent on postmenstrual age (PMA)) or standard regimen (no loading dose; a 10±2 day course at 15 mg/kg q24h, q12h, or q8h). The primary endpoint was successful outcome at end of vancomycin therapy (EVT) and no clinically/microbiologically significant relapse/new infection requiring anti-staphylococcal antibiotics within 10 days of EVT. Non-inferiority margin was –10%. Secondary endpoints included abnormal hearing screening. Recruitment stopped at 242 (120 optimised arm; 122 standard arm) infants; it was not possible to reach the sample size of 300 within remaining trial timelines. Trial registration: ClinicalTrials.gov (NCT02790996).

Findings 64/90 (71%) infants in the optimised and 73/92 (79%) in the standard arm (per-protocol analysis) had a successful primary outcome; non-inferiority was not confirmed (adjusted risk difference –7% 95% CI –15% to +2%). Incomplete resolution of clinical/laboratory signs after 5±1 days of vancomycin therapy was the main factor contributing to failure in the optimised arm. Hearing in the ITT population was abnormal in 25/84 (30%) infants in the optimised arm and 12/79 (15%) in the standard arm (adjusted risk ratio: 1·72; 95% CI (1·0–2·9).

Interpretation In the largest neonatal vancomycin efficacy trial yet conducted, no clear clinical impact of shorter duration was demonstrated. The use of the optimised regimen cannot be recommended as a potential hearing safety signal was identified; long-term follow-up will be conducted. These results emphasise the importance of robust clinical safety assessments of novel antibiotic dosing regimens in neonates.

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Background

Neonatal sepsis is a major public health concern, with ~3 million cases/year globally.[1] Coagulase negative staphylococci (CoNS) are skin and gut commensals and the most commonly isolated organisms in late onset sepsis (LOS) in high income countries,[2] particularly in association with central lines. Although overall CoNS LOS mortality rates are low,[3] CoNS sepsis is associated with neurodevelopmental sequelae.[4] CoNS are often multi-drug resistant[5] and the emergence of vancomycin heteroresistant organisms globally is concerning; these organisms are increasingly reported in neonates.[6,7]

Vancomycin is the most widely used antibiotic for Gram-positive LOS.[8] Neonatal vancomycin dosing and durations vary markedly,[9] leading to different drug exposures.[10] Robust infant pharmacokinetic (PK), safety and clinical efficacy data, for different dosing strategies, are lacking.[11] The NeoVanc project addressed this gap.

Pre-clinical components of the NeoVanc Programme included hollow-fibre infection (HFI) and rabbit models and a population PK meta-analysis (Supplementary Figure 1, appendix p 4). This work and a clinical bridging study determined that frequent dosing facilitated bacterial kill and led to quicker reduction in C-reactive protein whilst continuous infusions appeared to select for vancomycin heteroresistance.[12] The neonatal PK model suggested standard dosing regimens had low vancomycin target attainment and supported the use of a loading dose, to shorten the time to achieving therapeutic levels when combined with more frequent dosing in infants <29 weeks postmenstrual age (PMA).[13] Both the NICU bridging study and PK model indicated the need for more frequent dosing in infants <29 weeks PMA, where it can take days to achieve therapeutic levels. A vancomycin loading dose is routine in adults and has been used in neonates in association with continuous infusions[14], however, it is novel within the context of intermittent dosing. The subsequent optimised dosing regimen for the NeoVanc RCT was a short course (5±1 days) of vancomycin with a loading dose and more frequent dosing in infants <29 weeks PMA compared to a standard of care regimen of 10±2 days. Shorter vancomycin durations are supported by retrospective analyses.[15] A non-inferiority design was selected as shorter treatment duration was not expected to lead to higher efficacy than longer treatment duration but result in potential secondary benefits, including reduced rates of antimicrobial resistance and toxicity, because of lower overall vancomycin exposure.

Potential toxicity of vancomycin includes nephrotoxicity and ototoxicity. Neonatal vancomycin safety studies have historically been underpowered and relied upon retrospective analyses of routinely collected data.[16] Robust, pre-clinical neonatal vancomycin ototoxicity models are lacking.[16]

The NeoVanc RCT aimed to use a loading dose of vancomycin to provide faster target attainment with a new, shorter optimised regimen, thus reducing overall vancomycin exposure without affecting clinical efficacy or increasing toxicity when compared to the standard dosing regimen in infants with LOS known or suspected to be caused by Gram-positive microorganisms. The overall aim was to test whether the optimised regimen, which included a loading dose, was non-inferior to the standard regimen.

Methods

Study design

NeoVanc was an open-label, multi-centre, Phase IIb, randomised, active control, parallel group, non-inferiority trial recruiting participants across 22 NICUs in 5 European countries – Greece, Italy, Estonia, Spain and the United Kingdom. All were tertiary NICUs prescribing vancomycin routinely and selected to ensure representation of variation in neonatal intensive care practice across Europe.

NeoVanc was approved by the London–West London & GTAC Research Ethics Committee (REC reference: [16]/LO/1026) on 18th July 2016. Protocol amendments are outlined in the appendix (p 3). Ethics Committee and Regulatory Body approvals were gained in each participating country/hospital. Written, informed consent was obtained from all participants' parents/guardians by trained research personnel. Consent could be obtained if <24 hours of antibiotics had been administered in the current sepsis episode. Pre-consent was also allowed provided consent was re-confirmed if the infant became unwell. The study was performed in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines, local regulations and study standard operating procedures.

Participants

The protocol has been published elsewhere.[17] Briefly, infants were eligible for inclusion if they had a postnatal age of ≥72 hours and <90 days at randomisation and had clinical sepsis or blood culture positive sepsis. Modified EMA criteria were applied to identify clinical sepsis;[18] enrolment required ≥3 clinical or laboratory criteria or a positive culture with Gram-positive bacteria from a normally sterile site and ≥1 clinical or laboratory criterion, in the 24 hours prior to randomisation. Trial inclusion and exclusion criteria and post-randomisation exclusions from efficacy analysis are detailed in Supplementary Table 1 (appendix pp 5–6). Any infant who received ≥1 dose of study vancomycin was followed-up for safety.

Randomisation, minimisation and masking

Infants were randomised in a 1:1 allocation ratio for each regimen. A secure, web-based system (ClinInfo SAS Lyon, France), was adopted for randomisation, which was controlled through an authorised username and password. Infants were recruited and randomised by trained investigators at each site. A minimisation algorithm ensured balance between arms in relation to

baseline data – NICU, PMA, and presence/absence of an umbilical catheter/central line. Local investigators and parents/guardians were not blinded to regimen allocation. The trial management group and trial data analysts were blinded to aggregate outcomes apart from statisticians who were unblinded for interim analyses and Independent Data Monitoring Committee (IDMC) meetings.

Data management

Data were collected in an electronic case report form (eCRF) managed by Consorzio per Valutazioni Biologiche e Farmacologiche (Pavia, Italy). All collected data remained strictly confidential and anonymous.

Procedures

Infants received either the standard regimen: a 10±2 day course of 15 mg/kg q24h (PMA <29 weeks), q12h (PMA 29–35 weeks) or q8h (PMA >35 weeks), or the optimised regimen: a 5±1 day course of a single loading dose of 25 mg/kg followed by a maintenance dose of 15 mg/kg q12h (PMA ≤35 weeks) or q8h (PMA >35 weeks). Vancomycin hydrochloride (supplied by Laboratorio Reig Jofre, Barcelona, Spain) was administered intravenously via 60-minute infusion. In the optimised arm, the first maintenance dose was administered 8 or 12 hours after the loading dose, dependent on PMA; infants, therefore, received 10 mg/kg plus the 15 mg/kg maintenance dose (25 mg/kg in total as a "loading dose") as their first dose compared to the first maintenance dose of 15mg/kg in the standard arm. Vancomycin durations outside the specified limits were permitted based on clinician assessment. The standard treatment regimen was based on European dosing recommendations[19], with the 10±2 day duration being chosen to best-reflect current practice across European NICUs from pre-trial surveys, as no reference information from RCTs was available. Dose adjustments were permitted through routine therapeutic drug monitoring (TDM) or renal impairment, where modifications were made based on vancomycin levels and local policy.

Study visits are specified in Supplementary Table 2 (appendix pp 7–8). Clinical and laboratory parameters were monitored in accordance with the modified EMA neonatal sepsis criteria, at Day 3, Day 5±1 and Day 10±2 (standard arm or if still receiving study vancomycin only).[18] At the end of actual vancomycin therapy (EVT), improvement in overall clinical status was assessed, as defined in the protocol. Infants fulfilling these criteria proceeded to test of cure (TOC; primary endpoint visit),

10±1 days after EVT, where clinically significant new infections, microbiological relapse and/or microbiological new infections were recorded (Supplementary Table 3, appendix pp 9–11). Relapse/new infections were assessed at a short-term follow-up (STFU) visit at 30±5 days from initiation of study vancomycin.

Hearing screening was performed between EVT and 90 days after randomisation. Otoacoustic emissions (OAE) and/or auditory brainstem responses (ABR) were permitted as per local clinical practice; abnormal hearing was defined as no clear response in one ear on OAE or ABR.

Outcomes

Given the low mortality in CoNS sepsis, the primary outcome was based on clinical recovery, defined using modified EMA guidance[18] and expert consensus, as success at the test of cure (TOC) visit (10±1 days after EVT) in the per protocol population. Primary outcome success components were: participant was alive at TOC; participant had a successful outcome at EVT; participant had not had a clinically/microbiologically significant relapse/new infection requiring treatment with vancomycin or other specific anti-staphylococcal antibiotic (flucloxacillin, oxacillin, linezolid, tedizolid, daptomycin or teicoplanin) for >24 hours. Success at EVT was defined as participant was alive, there was a significant improvement in participant's overall clinical status, microbiological resolution or presumed eradication of bacteria and no new vancomycin-susceptible pathogens were identified (Supplementary Table 3, appendix pp 9–11). Success was evaluated using a clinical algorithm (Supplementary Table 3, appendix pp 9–11) that did not rely on physician assessment of outcome.

Secondary efficacy outcomes were: success at 5±1 days from initiation of study vancomycin; success at EVT; success at end of allocated therapy (EOAT; pre-specified in the Statistical Analysis Plan (SAP)); failure at TOC visit due to clinically/microbiologically significant relapse/new infection requiring treatment with non-anti-staphylococcal ("other") antibiotics for >24 hours; and failure at STFU.

Other secondary PK and microbiology outcomes will be reported separately when laboratory results are available.

Safety and adverse event assessment

Secondary safety outcomes included: abnormal renal function at STFU (urinary output <0.7 mL/kg/hours for 24 hours and/or creatinine value ≥100 µmol/L (≥1.13 mg/dL)); abnormal hearing screening tests after EVT; adverse events (AEs) up to STFU; vancomycin-related AEs; all serious adverse events (SAEs); and vancomycin-related SAEs. All AEs and SAEs occurring between the administration of the first dose of study vancomycin and the final follow-up visit were recorded in the eCRF.

Sample size

In total, 150 infants per arm provided at least 90% power to demonstrate non-inferiority using a two-sided 95% confidence interval (i.e. type I error rate of 2.5%), assuming a success rate in both arms of 95% and a non-inferiority margin on the risk-difference scale of 10% (Wilson-score method (nQuery. Statistical Solutions Ltd., Cork, Ireland)). A 5% relapse/new infection rate was based on data from neonIN, an international neonatal infection surveillance network and the magnitude of a clinically relevant effect was obtained through consensus in the NeoVanc Consortium. There is no regulatory guidance from either the U.S. Food and Drug Administration (FDA) or the EMA on neonatal sepsis trials, although a non-inferiority margin of 10% has been recommended by the FDA for acute pneumonia RCTs where treatment is believed to be highly efficacious.[20] The 10% non-inferiority margin was based on relapse/new infection and is in-keeping with adult antibiotic RCTs.[21,22] A power sensitivity analysis, without reference to the data, was performed when it became apparent that this sample size would not be met within the project timelines. This analysis indicated there would not be an appreciable increase in power gained from the expected sample size of 100 per arm (expected power = 83% using the same parameters as the original sample size calculation) to the maximum possible sample sizes, given resource and time limitations (power = 87% for 110 per arm). An IDMC reviewed the data periodically and the trial was consequently stopped before the planned recruitment target was met.

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Statistical analysis

The intention to treat population (ITT) comprised all randomised infants except post-randomisation exclusions and where consent to use data had subsequently been withdrawn (safety analysis population). The per protocol (PP) population (efficacy analyses) additionally excluded infants randomised in error, with a loading dose not administered as randomised, or duration of

vancomycin <48 hours from initiation of study vancomycin. The primary analysis used binomial regression with an identity link to report risk difference and associated 95% CI, with a non-inferiority margin of –10%. Inference was based on adjusted estimates, where PMA (<29 weeks/29-35 weeks/>35 weeks), and presence/absence of umbilical catheters/central venous lines were fixed effects and centre was a random effect. Three separate subgroup analyses were pre-specified: PMA at randomisation (<29 weeks, 29–35 weeks, >35 weeks); birthweight (<1000 g, 1000–1500 g, >1500 g); and presence or absence of an umbilical catheter/central venous line at the onset of sepsis. Bayesian analysis, pre-specified in the SAP, was used to estimate the probability of the optimised regimen truly being superior to the standard regimen under different prior assumptions (Supplementary Table 4, appendix p 11).

Analyses of secondary outcomes used risk ratios and their 95% confidence intervals from log binomial regression models, with the same adjustment factors as the primary outcome, except AEs and SAEs which were reported as the incidence rate per 1000 child days (number of infant-days recorded as alive and in the study between randomisation and STFU) with comparison using incidence rate ratios and 95% confidence intervals to allow for the possibility of multiple events occurring in the same infant and negative binomial regression to account for overdispersion. Post-hoc imputation was carried out on rates of abnormal hearing due to missing data; imputation was done separately for each arm and factors included in the model were baseline variables of PMA stratum, birthweight stratum (as above), presence or absence of umbilical catheters/central venous lines, sex, hypoxic ischaemic encephalopathy, intraventricular haemorrhage and presence/ absence of separate known risk-factor antibiotics (amikacin, ciprofloxacin, gentamicin, linezolid, netilmicin, and teicoplanin). For all analyses, 95% confidence intervals were used with no adjustment for multiple testing. Statistical analyses used Stata version 16 (StataCorp, College Station, Texas, USA).

Independent Data Monitoring Committee

An IDMC, composed of a neonatologist, microbiologist and statistician met three times throughout the trial period to monitor progress, efficacy, safety and pharmacokinetic data according to a specific Charter and without formal stopping guidelines.

Trial registration

NeoVanc was registered on ClinicalTrials.gov (NCT02790996) on 7th April 2016 and EudraCT (2015–000203-89) on 18th July 2016.

Role of the funding source

This research was funded by the European Union Seventh Framework Programme for research, technological development and demonstration under Grant No 602041. The funder had no role in study design, data collection, analysis or interpretation or writing of the report.

Results

Between 3rd March 2017 and 29th July 2019, 242 infants were randomised at 17 sites (Figure 1). Primary outcome data in the per protocol population were available for 90 infants in the optimised arm and 92 in the standard arm.

Baseline characteristics were broadly similar across arms (Table 1 and Supplementary Table 5, appendix pp 12–13). The great majority of infants (99%) had at least three clinical or laboratory signs of neonatal sepsis at baseline. A total of 80 Gram-positive bacteria were detected at baseline in 76 infants (69% *Staphylococcus epidermidis*, 10% *Staphylococcus hominis*, 9% *Staphylococcus haemolyticus*, with the remaining 12% comprising six different species (Supplementary Table 6, appendix p 13). *S. epidermidis* was relatively more common in the standard arm (34/43 (79%)) than in the optimised arm (21/37 (57%)), with *S. hominis* being relatively more common in the optimised arm (5/37 (14%) vs 3/43 (7%)); other organisms were comparable between arms. No invasive organism exhibited vancomycin resistance by EUCAST breakpoints. 101/116 (87%) available CoNS blood culture isolates demonstrated vancomycin heteroresistance by the brain heart infusion agar method [23] (51 standard arm and 50 optimised arm).

64% of infants in the optimised arm and 88% in the standard arm received vancomycin within their randomised duration window.

Continued treatment with vancomycin or another anti-staphylococcal antibiotic, likely reflecting treatment for the original infection, lasted a median of 6 days from commencement of study

vancomycin in the optimised and 10 days in the standard arm (Figure 2; Supplementary Table 7, appendix p 14). However, the difference between treatment arms became notably less when considering the total days of exposure to STFU, both of vancomycin (median of 7 days in the optimised arm and 10 days in the standard arm) and all antibiotics (median of 12 days in optimised arm and 11 days in standard arm; Figure 2; Supplementary Table 7, appendix p 14). TDM was assessed for 46 infants (25%) in seven centres, with 50% of assessed participants having at least one dosing adjustment (Supplementary Table 8, appendix p 14); assessment rates were slightly higher in the standard arm than the optimised arm.

Efficacy

A successful primary outcome was achieved in 137/182 (75%) infants: 64/90 (71%) in the optimised and 73/92 (79%) in the standard arm (Table 2). The adjusted risk difference between arms was –7% (95%CI = (–15%, 2%) and consequently non-inferiority was not concluded based on a non-inferiority margin of –10% (see Supplementary Table 9 for analysis of ITT population, appendix p 15). The lower success rate in the optimised arm seemed to be driven by higher apparent clinical failure rates at EVT when vancomycin therapy was stopped (21% in the optimised arm, at approximately Day 5, and 10% in the standard arm, at approximately Day 10; Table 2; Figure 3; Supplementary Figure 2, appendix p 15). Of those 28 infants with clinical failure at EVT, 57% had at least three clinical signs and 79% had at least one laboratory sign. Bayesian analysis showed 79%–99% probability that the optimised arm was truly worse than the standard arm, depending on the prior used, and 4%–43% probability that the optimised arm was truly worse than the standard arm by at least the 10% non-inferiority margin (Supplementary Table 10, appendix p 16; Supplementary Figure 3, appendix p 17). There was no evidence of heterogeneity in subgroup analyses (PMA, birthweight, presence of a central line) for the primary outcome (Supplementary Table 11, appendix p 17).

Secondary efficacy outcomes are outlined for the PP population in Table 2 and for the ITT population in Supplementary Table 9, appendix p 15. Success rates at Day 5±1 were lower in the optimised arm (71%) than in the standard arm (82%), although the 95% confidence interval crossed one (adjusted risk ratio: 0·90; 95%CI = (0·78, 1·04)) and post-hoc analyses as per primary outcome did not conclude non-inferiority (adjusted risk difference: –8%; 95% CI = (–19%, +3%)). Lower rates of relapse/new infections treated with non-anti-staphylococcal (“other”) antibiotics between EVT and TOC were seen in the optimised arm (3%) than in the standard arm (17%). When the primary outcome was extended to include relapse/new infections treated with any antibiotics between EVT and TOC,

there was no evidence success rates differed between the optimised (71%) and standard (74%) arms (adjusted risk ratio 0·98; 95% CI = (0·87, 1·11)) and post-hoc analyses as per the primary outcome was marginally non-inferior (adjusted risk difference: 3%; 95% CI (–10%, +6%)).

Toxicity and Safety

Abnormal hearing screening rates were twice as high in the optimised arm (30%) compared to the standard arm (15%; adjusted risk ratio = 1·93; 95% CI (1·10–3·39), p=0·02; Table 3), although only 82% of the ITT population had hearing assessed. Eleven of the 37 infants without hearing assessed had died and 70% of the remaining individuals were from two sites. Post-hoc multiple imputation (Supplementary Table 12, appendix p 18) indicated slightly higher rates of abnormal hearing in both arms (33% optimised and 19% standard adjusted risk ratio: 1·72; 95% CI (1·0–2·9)). Additional post-hoc analyses, on infants with available hearing screening results, showed higher rates of abnormal hearing in the optimised arm across all PMA groups but with weak evidence for a greater excess risk in those with the youngest PMA (Supplementary Table 13, appendix p 19), and across both hearing tests conducted (Supplementary Table 14, appendix p 19). There was no evidence that age at hearing test differed between arms (post-hoc analyses mean: 61 days (SD 30) in optimised arm, 62 days (SD 27) in standard arm; difference 1·6 days; 95% CI (–12, 9); p=0·77). Results were unchanged when repeated on the as-treated population (receiving loading dose as randomised; Supplementary Table 15, appendix p 19). Adding cumulative dose to the unadjusted model resulted in a very small decrease in the effect size although cumulative dose itself was not statistically significant (Supplementary Table 16, appendix p 20). Rates of abnormal renal function tests at STFU were extremely low, at 2% in the optimised arm and 0% in the standard arm (Table 3). There were 6 vancomycin related AEs in the optimised arm (1 SAE) and 4 in the standard arm (2 SAEs). There was no evidence that AEs and SAEs rates, both all-cause and vancomycin-related, differed across arms (Table 3).

Mortality

Eleven infants in the ITT population died (6 optimised and 5 standard arm): 4 with necrotising enterocolitis; 2 with Gram-negative infection; 3 with respiratory pathology; 1 with pericarditis and *S. epidermidis* bloodstream infection; 1 with severe brain injury secondary to vein of Galen aneurysm and septic shock.

Discussion

Main findings

NeoVanc, an open-label RCT, aimed to validate preclinical data to establish if the duration of vancomycin treatment for Gram-positive LOS could be safely reduced to 5±1 days with more frequent dosing in infants <29 weeks PMA and the inclusion of a loading dose. We could not conclude non-inferiority on the primary outcome. Additionally, a potential safety signal was detected in relation to higher abnormal hearing screening rates in the optimised arm.

The inability to conclude non-inferiority of the optimised arm in the primary outcome was multifactorial. The intended sample size was not reached which may have led to lack of power. In hindsight a non-inferiority limit of 10% of with an anticipated relapse rate of 5% could have been considered large. However, it did not impact on inference in the study. However, Bayesian analysis showed 79%–99% probability of the optimised arm being truly worse than the standard arm, implying low power may not be the only factor. Unsuccessful outcome in the optimised arm was predominantly related to lack of clinical recovery at EVT, and not because of relapse/new infection; 21% of infants (83% of failures) were clinical failures in the optimised arm compared to 10% of infants (47% of failures) in the standard arm. Microbiological failure was very low in both arms (1%), despite a Gram-positive blood culture positivity rate of >40% at baseline. The day of EVT differed between arms and secondary efficacy analyses showed higher failure rates in the optimised arm at the end of vancomycin therapy, both when therapy was randomised to end (EOAT) and when therapy actually ended (EVT). These differences may reflect the time taken for clinical/laboratory signs to normalise in infants with significant sepsis regardless of dosing regimen; assessment of both arms at Day 10±2 (EOAT in the standard arm) may have aided in elucidating this further. The new National Institute for Health and Care Excellence neonatal sepsis guidelines recommend 7 days of antibiotic treatment in babies with culture positive LOS.[24]

Only two infants demonstrated abnormal renal function at STFU. There was no evidence that the frequency of AEs and SAEs differed between study arms. Rates of abnormal hearing were almost twice as high in the optimised arm, although the associated 95% confidence interval were relatively wide and hearing screening results were only available for 82% of the ITT population. This result could reflect a genuine safety signal but may be due to low sample sizes and chance attributable to multiple testing. There was no evidence age at the time of hearing screening differed between arms.

Multiple imputation, factoring in other risk factors for hearing loss, including aminoglycoside and furosemide exposure and low birthweight, showed a slightly reduced effect size (1·7 times), smaller confidence intervals with the lower limit of the 95% confidence interval being 1.0 and consequently the pattern of missing data may be driving some of the differences observed. The protocol definition of abnormal hearing, was stricter than that used in clinical practice[25] so failure rates may be higher, although, would expect to be distributed evenly between arms. If genuine, the higher abnormal hearing screening rates in the optimised arm could be caused by either the loading dose or more frequent administration of vancomycin in infants <29 weeks PMA. There was weak evidence of an interaction between PMA group and arm on abnormal hearing screening rates, although sample sizes were low. Cumulative exposure of vancomycin has been described as a risk factor for abnormal hearing screening at NICU discharge in VLBW babies[26] although we did not find robust evidence of this. If the ototoxicity safety signal is being driven by the loading dose, then these NeoVanc results suggest cumulative dose is unlikely to be the only risk factor, particularly as the number of days of vancomycin exposure up to STFU was similar in both arms. Risk factors are likely to be cumulative and data on hearing outcomes in septic babies are sparse. Of note, a neonatal meropenem versus standard of care RCT reported abnormal hearing screening rates of up to 29% in their population of septic infants.[27] Robust, prospective long-term hearing data are required to ascertain if failure at hearing screening translates to long-term hearing loss on diagnostic auditory assessment.[16] A NeoVanc long-term follow-up study is planned with the aim of obtaining missing data and collecting follow-up hearing data in infants who failed their hearing screening.

Previous trials

Only two neonatal vancomycin RCTs have been registered on ClinicalTrials.gov and the International Standard Randomised Controlled Trial Number trial registry in the last 20 years, emphasising the paucity of efficacy trials.[28,29] Both trials were stopped prior to recruitment of their target sample size, demonstrating the difficulty of recruiting to neonatal antibiotic trials.

Trial strengths and limitations

CoNS sepsis has historically been considered to have a less severe clinical course. However, infants recruited into NeoVanc had significant clinical sepsis; 99% had ≥3 clinical/laboratory signs with blood culture positivity rate being high. The inclusion criteria clearly identified septic infants.

Test of cure assessment in neonatal antibiotic trials is not standardised and no guidance is available on neonatal sepsis trial design from the FDA and EMA.[30] Test of cure in NeoVanc was based on days from actual end of vancomycin therapy and not days from randomisation and so was at different timepoints in the optimised compared to the standard arm. Very low rates of new infection and relapse were seen in both arms. The NeoVanc trial was a pragmatic open-label study, and this may have influenced clinician decisions, particularly if they were accustomed to giving longer antibiotic course durations. The STFU visit was 30±5 days from randomisation to ensure comparability of outcome assessment with respect to the initial presenting episode and overall antibiotic exposure was comparable between arms to this timepoint, which supports lack of evidence of a difference between the arms at this later follow-up.

The NeoVanc Programme incorporated extensive pre-clinical studies[12] including the largest ever meta-analysis evaluating the vancomycin population PK in infants.[13] This RCT also provides valuable PK, safety and efficacy information on infants <29 weeks PMA, who comprised nearly a quarter of the study population.

Next steps

Interim NeoVanc PK analysis (full analysis delayed by the COVID-19 pandemic; to be published) indicate that the newly developed PK model from the pre-clinical studies, which has been externally validated, is robust, supporting the use of pre-clinical studies to optimise antimicrobial dosing regimens. However, modelling toxicity is more problematic and can only be detected within the context of a reasonably sized RCT. The ototoxicity safety signal, potentially associated with the loading dose in this RCT, was not predicted, particularly given the previous inconclusive data relating to ototoxicity in infants and considering a loading dose is recommended in critically ill children and adults.[31] Neonates may demonstrate unique toxicity profiles, and dosing recommendations should be adopted with caution if the data are generated from adult or childhood RCTs alone. Rates of ototoxicity have not been compared between continuous and intermittent vancomycin infusion within the setting of an RCT in infants.

Recruitment to neonatal antibiotic trials is challenging and the sample size required to detect safety signals is considerably more than most of the currently recruiting new neonatal antibiotic trials.[32] An approach that balances risk and unmet need seems appropriate. For antibiotics with a low risk

of toxicity (e.g. beta-lactams) and limited clinical unmet need, PK studies alone to determine optimal dosing regimens are reasonable. For drugs with a higher toxicity potential and high unmet clinical need, NeoVanc demonstrates that, robust RCTs adequately powered to identify potential novel toxicity signals may be required. Additionally, efficacy assessment should be undertaken at the same timepoint from randomisation in each arm to allow equal time for resolution of symptoms in both arms. We would not currently recommend a 25 mg/kg loading dose of vancomycin in infants or more frequent dosing in infants <29 weeks PMA in view of the identified hearing safety signal.

Contributors

Conceptualisation and funding acquisition – MAT, IL, ER, EJ-A, PTH, MS; study design – LFH, MAT, PTH, IL, EJ-A, ER, MS; methodology – LFH, MAT, PTH, IL, EJ-A, ER, MS, MNC, LR; data curation – MNC; data analysis – MNC, LFH, ASW, MS; project administration – LFH, DD, LR; resources – LFH, DD, LR; investigation –CA-D, EB, AD, M-LI, AM, TM, GM, VP, KS; supervision – LFH, MS, MAT, DD, IL, PTH, ER, LR, CA-D, EB, AD, M-LI, AM, TM, GM, VP, KS; visualisation – LFH, MNC, MS; software and validation – MNC; writing - first draft – LFH, MNC, MS; writing – review and editing – LFH, MNC, MS, MAT, DD, IL, ER, PTH, EJ-A, LR, CA-D, EB, AD, M-LI, AM, TM, GM, VP, KS, ASW

LFH* – trial coordinator, MNC* – trial statistician, MS – chief investigator, country coordinators – MAT, IL, ER, CA-D, AD

*LFH and MNC have contributed equally and are co-first authors

LFH and MNC verified the underlying data.

All authors had access to the full data set and accept responsibility to submit for publication.

Declarations of interests

PTH is a member of the National Institute for Health and Care Excellence neonatal infection guideline development group. LR is an employee of Therakind Ltd. DD's PhD was funded by Fondazione Penta – ONLUS; the capacity and remit of his PhD was independent and unrelated to his involvement with NeoVanc.

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Data sharing

The study protocol has previously been published in detail.[17] Sharing of data will be considered based on a detailed proposal which should include aims, methods and a statistical analysis plan. Requests will be checked for compatibility with regulatory and ethics committee requirements as well as with compatibility with the participant informed consent. Proposals should be addressed to the corresponding author at lhill@sgul.ac.uk and will be evaluated by the Sponsor.

Research in context

Evidence before this study

Neonatal sepsis is a global health priority. Coagulase negative staphylococci (CoNS) are the most commonly identified organisms in neonatal late onset sepsis (LOS) in high income countries, with very low birthweight babies experiencing the greatest associated morbidity and mortality. Vancomycin is the mainstay of treatment of CoNS LOS. Prior to the initiation of this trial, a search of PubMed, ClinicalTrials.gov and ISRCTN identified only two neonatal vancomycin randomised controlled trials (RCTs) registered in the last 20 years. These two RCTs, recruited a total of 220 babies; one was an active control trial comparing cefazolin and vancomycin and the other compared continuous and intermittent infusion with pharmacokinetic endpoints.

The NeoVanc Programme completed pre-clinical studies, which informed the optimised dosing regimen evaluated in the RCT. The NeoVanc hollow fibre infection and animal models determined that more frequent dosing may be beneficial in facilitating bacterial kill and discouraging the development of vancomycin resistance. A bridging study to the NICU clinical setting, established that more frequent dosing led to a quicker and more satisfactory reduction in C-reactive protein, particularly in infants <29 weeks postmenstrual age (PMA), and supported a shorter vancomycin course. Linder, *et al* previously found, in a retrospective study, that infants with an uncomplicated clinical course treated for CoNS sepsis with vancomycin for 5 days after the last positive blood

culture, had similar outcomes to those treated for longer durations. A novel neonatal vancomycin PK model was developed within the NeoVanc programme based on a population PK metanalysis from previously published data. It included 4894 vancomycin concentrations from 1631 neonates and supported the need for more frequent dosing in infants <29 weeks PMA and predicted an optimised regimen which included a 25 mg/kg loading dose. The use of a loading dose of 25 mg/kg in seriously unwell adults and children has been supported by the Infectious Diseases Society of America in the treatment of MRSA.

Added value of this study

NeoVanc is the first RCT to evaluate a loading dose of vancomycin in conjunction with intermittent dosing in neonatal sepsis and the largest neonatal vancomycin clinical efficacy trial ever conducted. However, NeoVanc identified an ototoxicity safety signal, potentially associated with the use of a loading dose and/or more frequent dosing in infants <29 weeks PMA, which has not been previously recognised in this population. Additionally, no clear advantage was seen for adopting a shorter 5±1 day course over a standard 10±2 day course for neonates with significant clinical sepsis. The adapted EMA neonatal sepsis criteria, utilised for inclusion to the RCT, successfully identified such infants with significant clinical sepsis, with >40% of baseline blood cultures positive in trial participants.

Implications of all the available evidence

There is no evidence for reducing vancomycin course duration to 5±1 days in truly septic infants as no benefit was identified. A vancomycin loading dose and more frequent dosing in infants <29 weeks PMA should not currently be recommended in infants because of a possible ototoxicity safety signal. Long-term neonatal vancomycin hearing analyses are in progress.

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