BMJ Open

Inguinal hernia repair in preterm neonates: is there evidence that spinal or general anaesthesia is the better option regarding intraoperative and postoperative complications? A systematic review and meta-analysis

Katharina Dohms ,[1] Marc Hein,[1] Rolf Rossaint,[1] Mark Coburn,[1] Christian Stoppe,[2] Constanze Barbara Ehret,[1] Tanja Berger,[3] Gereon Schälte[1]

To cite: Dohms K, Hein M, Rossaint R, *et al*. Inguinal hernia repair in preterm neonates: is there evidence that spinal or general anaesthesia is the better option regarding intraoperative and postoperative complications? A systematic review and meta-analysis. *BMJ Open* 2019;**9**:e028728. doi:10.1136/bmjopen-2018-028728

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-028728).

Received 29 December 2018
Revised 21 August 2019
Accepted 12 September 2019

For numbered affiliations see end of article.

Correspondence to
Dr Gereon Schälte;
gschaelte@ukaachen.de

ABSTRACT

Objectives Whether spinal anaesthesia (SA) reduces intraoperative and postoperative complications compared with general anaesthesia (GA) was investigated.

Design The meta-analysis was structured based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Databases (PubMed, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science) were searched, and four randomised controlled trials (RCTs) and two retrospective cohort studies were included. A random-effects model with pooled risk ratios and mean differences with 95% CIs were used. Statistical heterogeneity was evaluated using the I^2 statistic. Quality assessment of the studies was performed by assessing the risk of bias according to the Cochrane and GRADE methodology.

Setting Publications from January 1990 to November 2018 were included.

Participants and interventions Our study selection captured information from studies focusing on neonates born before the 37th gestational week who were scheduled for an inguinal hernia repair operation under either SA or GA.

Primary and secondary outcome measures The primary outcome measures were apnoea, postoperative ventilation and method failure rates according to predefined eligibility criteria. The duration of surgery, desaturation events <80%, hospital stay duration and postoperative bradycardia were secondary outcomes.

Results We found significantly fewer events for the outcomes 'any episode of apnoea' and 'mechanical ventilation postoperatively' in the SA group. Bradycardias were significantly less common in the SA group. In total, 7.5% of the SA group were converted to GA. The duration of surgery was significantly shorter in the SA group. No significant differences were found in the outcome measures 'postoperative oxygen supplementation', 'prolonged apnoea', 'postoperative oxygen desaturation <80%' and 'hospital stay'.

Conclusions We consider SA a convenient alternative for hernia repair in preterm infants, providing more safety regarding postoperative apnoea. To the best of our knowledge, this is the first meta-analysis to include studies exclusively comparing SA versus GA. More high-quality RCTs are needed.

Trial registration number CRD42016048683

Strengths and limitations of this study

- ► This systematic review and meta-analysis was based on a rigorous search of the literature with maximum efficiency by combining an initial focused search with a subsequent follow-up search.
- ► All specified outcome parameters were audited independently by two persons.
- ► Our synthesis approach used a mixture of description and tabulation to summarise the evidence, including the strength of evidence and risk of bias.
- ► So far, unpublished post hoc data were analysed and resulting findings are provided to ensure best evidence.
- ► All included studies varied and were not homogeneous concerning the spinal anaesthesia and general anaesthesia techniques and the published haemodynamic and outcome measures.

INTRODUCTION

Spinal anaesthesia (SA) is a fast, simple and cost-effective method that has been used for the performance of inguinal hernias since the beginning of the 20th century.[1] As it has become more established in recent years, the relevant technical skills and knowledge have matured. Thus, it is of great interest to investigate this specific local technique and compare it to the commonly used general anaesthesia (GA), which has also been under consideration in recent years due to possible damaging side effects.[2–5] In neonates, GA is

associated with a high risk of complications, such as bradycardia and apnoea,[6] whereas SA may involve far fewer side effects. Nevertheless, GA remains the preferred choice.[7] Over the last few decades, improved neonatal care has led to a significant increase in the survival of neonates delivered preterm.[8 9] Prematurity is the largest risk factor for inguinal hernias, which need to be repaired at an early age.[10–12] Moreover, preterm-born neonates are more likely to have pre-existing diseases such as bronchopulmonary dysplasia, which puts them at an even higher risk for developing complications. In addition, gestational age and apnoea are inversely proportionally related. Due to the increasing obligation to intervene via herniorrhaphy, investigating whether any of the common anaesthetic procedures offer advantages in this context is of paramount interest.[10] Our aim was to assess which anaesthetic technique could provide better patient safety outcomes.

In this meta-analysis, we systematically analysed the current literature on SA versus GA for inguinal hernia repair in neonates born before the 37th gestational week. We looked at the incidence of apnoea, the need for postoperative ventilation, the incidence of failure of SA and more outcome parameters.

METHODS

This meta-analysis and systematic review was based on the guidelines of the 'Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols' (PRISMA-P) statement.[13]

Information sources and search strategy

The PubMed, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science databases were screened for relevant publications in all languages up to November 2018. The search terms were "Hernia, Inguinal/surgery" AND "(Infant OR preterm infant)" AND "(Anaesthesia, General OR Anaesthesia, Spinal)" (online supplementary figure 1). The search terms were constructed conforming to the PICOS framework to achieve the best search result (online supplementary figure 2). Additionally, the reference lists of eligible studies were screened. All databases were independently screened by KD and GS, and the results were compared.

Study selection and eligibility criteria

Our study selection captured information from studies focusing on neonates born before the 37th gestational week who were scheduled for an inguinal hernia repair operation under either SA or GA. Due to the small number of randomised controlled trials (RCTs), retrospective cohort studies (RCSs) were also included. The primary outcome measures were apnoea, postoperative ventilation and method failure rates according to predefined eligibility criteria. Duplicate sources were excluded. Irrelevant sources were eliminated based on their abstracts and titles. The full texts of the remaining articles were analysed and re-evaluated. A flow diagram

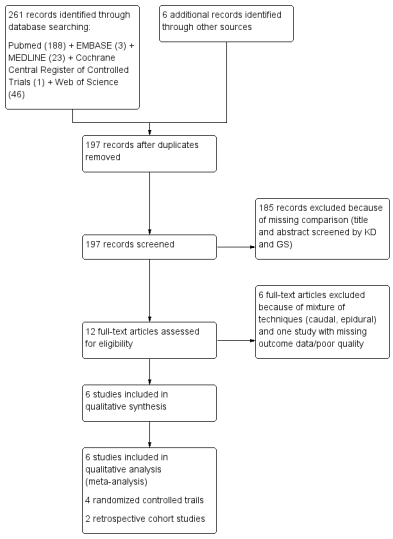

Figure 1 Flow diagram of the meta-analysis based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

based on the PRISMA statement depicting the study selection process was constructed (figure 1).

Some studies compared a mixed dataset of regional anaesthesia (ilioinguinal, caudal, etc) to GA.[14–18] To gather information on the subgroups and include it in our analysis, we contacted the authors. Therefore, we were able to apply our inclusion criteria and to include the subgroup data from the GAS trial.[17]

Patient and public involvement

Due to the methodology of this trial, neither the patients nor the public were directly involved in the research question, selection of the outcome measures, design and implementation of the study or the interpretation of the results.

Data collection process and data items

After the final sources were defined, the baseline characteristics were compiled in a database showing the name of the study, year of publication, first author, study design, number of patients, sex of the patients, postconceptional age, body weights, type of anaesthesia and anaesthetics used, pre-existing lung conditions, whether supplementary oxygen was required before surgery and whether supplemental medication was administered, for example, pain medication.

The following outcomes were collected independently by KD and GS: episodes of postoperative apnoea, need for postoperative mechanical ventilation and incidence of failure of SA as primary outcomes and the duration of surgery, desaturation events <80%, hospital stay duration and postoperative bradycardia as secondary outcomes.

The hospital stay duration was calculated based on the raw data in Somri *et al*.[19] Pre-existing lung condition formed a supergroup for respiratory distress syndrome and a history of preoperative apnoea. Focusing on the GAS trial, we grouped all patients who ever received an

endotracheal tube, methylxanthine or continuous positive airway pressure preoperatively.

Risk of bias

Review Manager (RevMan) software (Cochrane Collaboration, London, UK) was used to perform the risk of bias analysis in individual studies in the following domains: selection bias, performance bias, detection bias, attrition bias and reporting bias.[20] Each study was analysed individually for these biases by KD and GS.

Publication bias is usually evaluated by a funnel plot or by further analysis, such as Egger's and Begg's tests. Funnel plots require a minimum of 10 studies for safe interpretation. Another option for evaluating publication bias is to analyse small-study effects. Small studies are often associated with more decisive treatment effects caused by publication bias.[21] To focus on these potential effects, we looked for evidence concerning selective reporting and the selection criteria for patient populations. Selective reporting was evaluated by missing outcome data and the emphasis of non-significant outcomes.

GRADE methodology (GRADEpro, Version 20; McMaster University, 2014) was used to assess the quality of evidence across studies.[22 23]

Statistical analysis

RevMan version 5.3 was used to perform the statistical analyses of the selected data (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).[20] The Department of Medical Statistics of the RWTH Aachen University, Aachen, Germany, supervised the methodology of the statistical analysis.

Descriptive measures, such as rates (means, SD) and their corresponding 95% CIs, were calculated using MedCalc Statistical Software for Windows, version 16.8 (MedCalc Software, Ostend, Belgium). The outcome effects were either continuous or dichotomous and are depicted in forest plots. Effect measure estimates were calculated as the mean differences (MDs) for all continuous variables and as risk ratios (RRs) for dichotomous variables with 95% CIs in a random effects model.[24 25] For the MDs, we applied the inverse variance method.

Across studies, heterogeneity was determined to detect whether the results of both groups were comparable. To quantify heterogeneity, we used the I^2 statistic following the Higgins and Thompson method.[26 27] Heterogeneity was noted as substantial if I^2 was >50% and was mentioned in our results. When heterogeneity was detected, a sensitivity analysis was performed to identify possible reasons. We considered p-values <0.05 as statistically significant. The null hypothesis was tested as a two-sided hypothesis that there was no difference in the outcome between GA and SA.

Single-zero studies were calculated assuming that 0.5 events occurred in the group.[28] To investigate whether double-zero studies, which were excluded in the analysis in RevMan, and the method of including single-zero studies via continuity corrections changed our results, we used the beta-binominal regression method in SAS (V.9.4; SAS Institute, Cary, North Carolina, USA) Macro (MA_DOUBLEZERO)[29] to reanalyse the data, and all differences are described in the following sections.

RESULTS

The database search yielded 261 studies, with 6 additional studies found in the reference lists (figure 1). After removing duplicates, 197 studies were screened by title and abstract, after which 10 articles remained. After applying the eligibility criteria, six studies (four RCTs and 2 RCSs) were ultimately identified. A total of 512 patients were included (226 patients with SA and 286 with GA).

Baseline characteristics

Table 1 shows the baseline characteristics of all included studies.

Risk of bias and GRADE

Our risk of bias analysis provides an indication of publication bias. All studies except Kim *et al*[30] and Lambertz *et al*[31] assigned the patients randomly to the groups, but the process of random sequence generation was described in only one study.[17] The participants were easily blinded because the surgery was performed on infants born preterm, but procedural blinding was not possible due to the anaesthetists' interventions. Somri *et al*[19] excluded three patients due to puncture failure and one patient due to hypothermia in the SA group. In one trial, patients were allocated to the GA group after unsuccessful puncture, and episodes of postoperative apnoea were reported in only the GA group.[32] Online supplementary figure 3 shows our risk of bias graph.

Very low quality evidence was detected for any episode of apnoea, and low quality evidence was detected for prolonged apnoea. Moderate quality of evidence was found for postoperative mechanical ventilation and bradycardias. The overall evidence quality was reduced because sequence generation was not described, and the sample sizes were small. Online supplementary table 1 shows the GRADE analysis table.

Primary outcomes

Complete failure of the method

Complete failure of the method was defined as a change from SA to GA at any point during surgery. In total, 7.5% (95% CI: 0.04 to 0.12) of the patients undergoing SA (15 of 200 patients) were converted to GA (online supplementary table 2). In total, 28% (95% CI: 0.21 to 0.37) received more than one puncture (54 of 191 patients)[17 19 33] and 16% (95% CI: 0.10 to 0.25) required supplemental anaesthesia (11 of 29 patients).[17 19 31] Davidson *et al*[17] reported one case of high spinal block that required manual ventilation.

Postoperative apnoea

The outcomes were grouped into (1) any episode of apnoea and (2) prolonged apnoea. Somri *et al*[19] and

Table 1 Baseline data of the included studies

Name, publication year	Type	Study design	n	Sex, male, n (%)	Gesta-tional age, mean (weeks) ±SD	Postconceptual age, mean (weeks)±SD	Presenting weight, mean (g)±SD	Type of anaesthetic	Pre-existing lung conditions,* n (%)	Required oxygen before surgery, n (%)	Supplemental medication PRO and IO (%)
Welborn *et al*, 1990[33]	SA	RCT	11	NA	31.3±2.6	43.3±3.9	NA	Tetracaine, epinephrine	3 (28)	NA	NOA
	GA		16	NA	31.8±3.9	40.5±3.4	NA	Halothane, N_2O/O_2	6 (38)	NA	NOA
Krane *et al*, 1995 [32]	SA	RCT	9	7 (78)	29.9±3.6	42.3±4.1	3300±700	Tetracaine	7 (78)	NA	N_2O IO; NOA
	GA		9	7 (78)	29.9±3.9	40.9±2.1	3270±2100	Halothane, N_2O	6 (67)	NA	NOA
Somri *et al*, 1998 [19]	SA	RCT	20	NA	33.1±4.0	43.7	3700±1100	Bupivacaine	8 (40)	6 (30)	PCM (20)
	GA		20	NA	32.7±3.2	44.15	3340±1376	FI: thiopental; FM: halothane; N_2O/O_2	6 (20)	NA	PCM (40)
Kim *et al*, 2003[30]	SA	RCS	15	NA	27.5±1.9	41.1±2.8	2937±755	Bupivacaine	15 (100)	15 (100)	Ketamine IO (73.3); oxygen IO (60)
	GA		14	NA	27.8±1.7	40.2±2.6	2806±541	FI: thiopental; FM: enflurane and N_2O/O_2	14 (100)	11 (79)	Ketamine IO;
Lambertz *et al*, 2014 [31]	SA	RCS	69	60 (87)	NA	NA	4047±1002	Bupivacaine	11 (16)†	NA	NA
	GA		31	26 (84)	NA	NA	5327±1376	FI: Propofol, piritramide; FM: propofol	3 (10)†	NA	Remifentanyl IO
Davidson *et al*, 2015[17]	SA	RCT	102	84 (82)	32.5±3.2	43.0±3.8	3633±919	(Levi-)Bupivacaine	55 (54)	46 (45)	NOA PRO (5); vasoactives IO (1.9); NOA PO (46); OA PO (0)
	GA		196	169 (86)	32.6±2.3	43.9±4.3	3891±1062	Sevoflurane	104 (53)	79 (40)	NOA PRO (8); vasoactives IO (6); NOA PO (32); OA PO (1); epinephrine PO (0.5)

*Patients with apnoea, IRDS, ever required mechanical ventilation or medication for apnoea before surgery.
†Pre-existing diseases.
FI, for introduction; FM, for maintenance; GA, general anaesthesia; IO, intraoperatively; NA, not answered; N_2O, nitrous oxide; NOA, non-opioid analgesics ; OA, opioid analgesics; PCM, paracetamol; PO, postoperatively; PRO, preoperatively; RCS, retrospective cohort study; RCT, randomised controlled trial; SA, spinal anaesthesia.

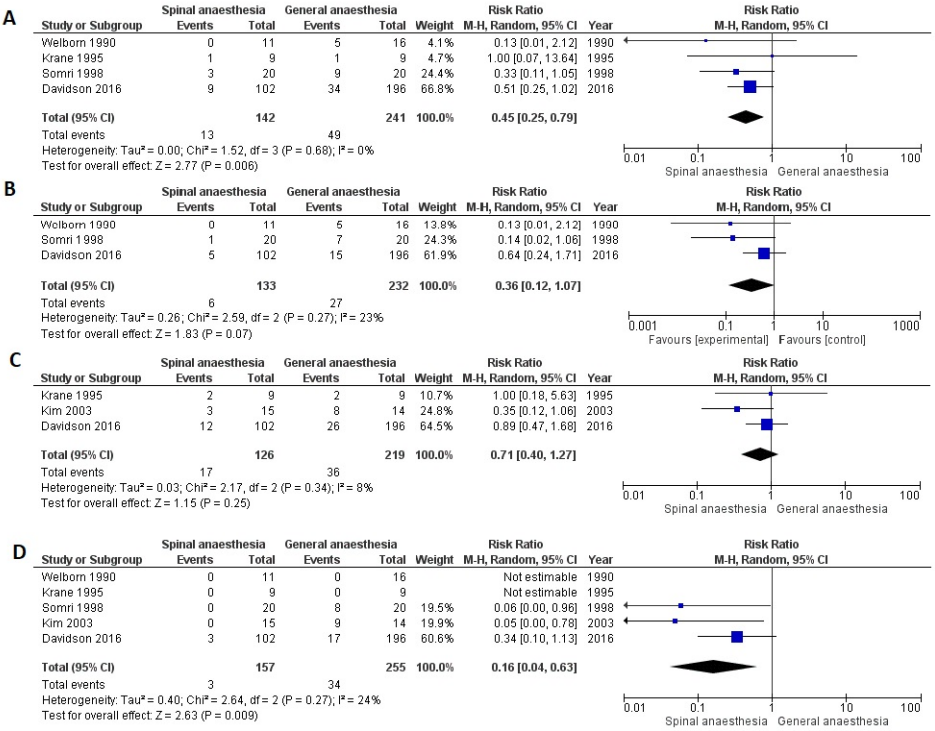

Figure 2 Postoperative apnoea: (A) any episode of apnoea, (B) prolonged apnoea, (C) postoperative oxygen supplementation, and (D) postoperative mechanical ventilation.

Welborn *et al*[33] defined short apnoea as a breathing pause for less than 15 s. Prolonged apnoea was defined as a breathing pause for longer than 15 s or shorter than 15 s if associated with bradycardia.[17 19 30] Krane *et al*[32] defined apnoea as a pause lasting from 11 to 15 s.

The analysis (figure 2A) showed that SA was significantly better than GA (RR 0.45 (95% CI: 0.25 to 0.79); p=0.006) for any episode of apnoea. In the SA group, 9% (95% CI: 0.05 to 0.16) of the patients (13 of 142 total patients) suffered from apnoea, whereas 20% (95% CI: 0.15 to 0.27) of the patients in the GA group experienced any episode of apnoea (49 of 241 total patients).

The item prolonged apnoea (figure 2B) did not reach a significant difference for any of the methods (RR 0.36 (95% CI: 0.12 to 1.10); p=0.07). It occurred in 4.5% (95% CI: 0.02 to 0.10) of the SA group (6 of 133 patients) and in 11.6% (95% CI: 0.10 to 0.20) of the GA group (27 of 232 patients).

Postoperative respiratory support

Respiratory support after surgery was subdivided into the need for oxygen supplementation and the need for mechanical ventilation in any form (nasal airway, Guedel tubus, endotracheal intubation, etc).

Patients requiring postoperative oxygen supplementation (figure 2C) were more common in the GA group, but this difference did not reach significance (RR 0.71 (95% CI: 0.40 to 1.27); p=0.25). In total, 13.5% (95% CI: 0.08 to 0.22) of the patients (17 of 126) in the SA group and 16.4% (95% CI: 0.12 to 0.23) of the patients (36 of 219) in the GA group required oxygen postoperatively.

Postoperative mechanical ventilation (figure 2D) was more frequent in the GA group (RR 0.16 (95% CI: 0.04 to 0.63); p=0.009). In total, 1.9% (95% CI: 0.004 to 0.06) of the patients in the SA group (3 of 157 patients) and 13% (95% CI: 0.04 to 0.18) of the patients (34 of 255) in the GA group needed mechanical ventilation after the operation.

Secondary outcomes

Desaturation <80%

Only Krane *et al*[32] defined a time period of at least 10 s and recorded the events for 12 hours. Davidson *et al*[17] continuously recorded desaturation in the first postoperative hour and noted it every 5 min.

With regard to obtaining a desaturation of <80% (events per patient), there was no significant advantage or disadvantage (RR 0.56 (95% CI: 0.30 to 1.03); p=0.06) of one method. However, 6% (95% CI: 0.03 to 0.13) of SA patients (7 of 111 patients) and 10% (95% CI: 0.06 to 0.15) of GA patients (20 of 205 patients) underwent desaturation <80%.

Hospital stay

The mean value and SD of the hospital stay were calculated from the raw data in Somri *et al*.[19] The hospital stay was shorter in the SA group,[19 32] but this difference was not significant (MD −0.42 (95% CI: −1.27 to 0.43); p=0.33). Heterogeneity was considerable (I^2=77%, p=0.01). Online supplementary figure 4 shows the results of the analysis.

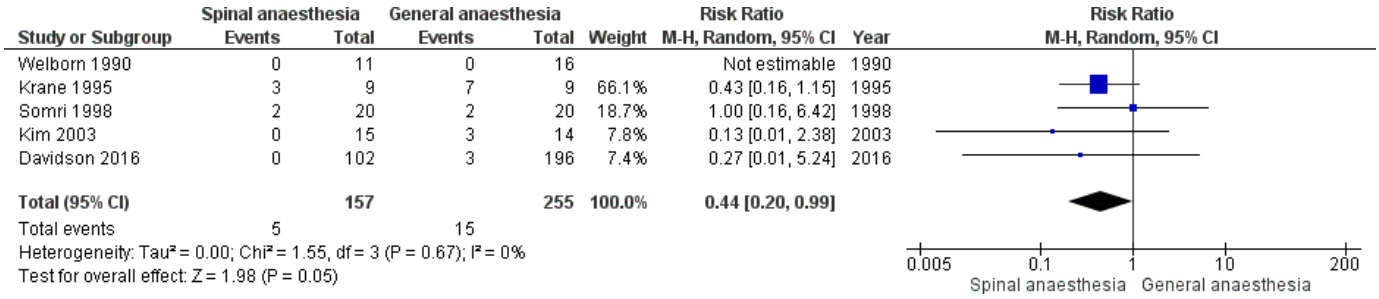

Figure 3 Postoperative bradycardia.

Bradycardia

Most of the studies defined bradycardia as fewer than 100 beats per minute,[17 19 30 32] although Krane *et al*[32] defined bradycardia as fewer than 80 beats per minute. Davidson *et al*[17] recorded heart rates continuously for the first postoperative hour, and heart rates were noted in a 5 min rhythm. Bradycardia appeared more frequently in the GA group (figure 3), with an occurrence of 5.8% (95% CI: 0.03 to 0.10, 15 of 255 patients), and a significant difference was found between groups (RR 0.44 (95% CI 0.20 to 0.99); p=0.05). In the SA group, 3.1% of the patients (95% CI: 0.01 to 0.07, 5 of 157 patients) had bradycardias.

Duration of surgery

The duration (online supplementary figure 5) was significantly shorter for surgeries performed under SA (MD −2.53 (95% CI: −4.93 to −0.12); p=0.04). Heterogeneity was detectable but under the level of significance (I^2=19%).

Additional analysis

Sensitivity analysis, single-zero and double-zero studies

Significant heterogeneity was detected for hospital stay duration (I^2=77%). The sensitivity analysis of the hospital stay revealed that lower heterogeneity occurred (I^2=42%) when Lambertz *et al*[31] was removed for this measure; however, excluding that study did not alter the fact that no significant difference between SA and GA was observed. The definition of hospital stay was not consistent, which was probably the main reason for the marked heterogeneity.

The outcome measures, including single-zero studies (any episode of apnoea and prolonged apnoea), were reanalysed using the SAS Macro as described, but the results equalled our primary results for both outcome measures. The double-zero outcome measures were also reanalysed using beta-binominal regression analysis in SAS. For the outcome measures, including double-zero studies (postoperative mechanical ventilation and bradycardia), the results changed such that by including the double-zero studies, no significant difference between SA and GA could be found (RR 0.17 (95% CI: 0.02 to 1.58), p=0.12; RR 0.41 (95% CI: 0.08 to 2.01), p=0.27).

DISCUSSION

The objective of this meta-analysis was to compile all data from trials comparing SA and GA for inguinal hernia repair and to assess whether SA or GA provided superior patient safety outcomes. The findings revealed significant benefits in terms of the outcome measures for SA in the postoperative time frame for any episode of apnoea, the need for mechanical ventilation, bradycardia and the duration of surgery. We did not find any differences between the groups for the postoperative outcomes of desaturation <80%, the need for oxygen supplementation, prolonged apnoea and hospital stay duration.

In our analysis, some important data could not be captured by a single endpoint outcome, for example, prolonged apnoea. In Davidson *et al*[17] in the SA group, prolonged apnoea was self-resolved or resolved through stimulation in 60% of patients, and 40% of prolonged apnoea was resolved through oxygen supplementation with or without mask ventilation. In the GA group, 17% of the patients who had prolonged apnoea experienced resolution of the apnoea by itself or through stimulation, whereas 83% of the patients received oxygen supplementation with or without mask ventilation. One of the patients in the GA group even underwent cardiopulmonary resuscitation. Our outcome of postoperative mechanical ventilation also showed a significant difference between the two groups. For apnoea, there were different endpoints of observation. Between 12 hours and 5 days postoperatively, 2.9% of patients (3 of 102 patients) in the SA group and 3% (6 of 196) in the GA group underwent interventions for apnoea.[17] No patients were intubated in this time frame, whereas in the GA group, one patient had to remain intubated. Many studies have emphasised the difficulty of monitoring apnoea events. Cote *et al*[34] noted that apnoea was recorded at a higher prevalence when the recording device was equipped with an alarm bell, which was used in only one trial. Das *et al*[35] observed that proper therapy for postoperative pain reduces instances of apnoea, and patients in the SA group required less pain medication than patients in the GA group.

There was a difference in the prehistory of apnoea between the two groups. Somri *et al*[19] reported that 3% of the patients, one patient in the SA group and three patients in the GA group, had a prior history of apnoea. Welborn *et al*[33] identified no patients with a prior history of apnoea in the SA group and 60% in the GA group. Davidson *et al*[17] reported that all patients had a prehistory of apnoea in the SA group, whereas only 79% of the

patients had a history of apnoea in the GA group. This parameter can likely never be controlled, but because lung condition is very important to the risk of developing a postoperative apnoea,[36 37] it might also influence the effect estimates. In addition, gestational age and apnoea are inversely proportionally related.[38]

In some studies,[31 32] patients received some sort of sedation in the SA group. While it is never possible to exclude the need for a sedative, as the aim should always be to provide the best care for the individual, the use of sedation might have restricted the effects of SA. Additionally, many of the anaesthetics used in our comparison studies are no longer state-of-the-art anaesthetics. Using older studies in our review might be an indication of inconsistency when considering the GRADE methodology tools. Nevertheless, we believe that, for this subpoint, it is still important to investigate possible side effects, as many of these anaesthetics are still used in Europe as well as in developing countries for cost-efficiency reasons.[39]

Each of the methods is linked to a certain special risk. For SA, it is possible to cause a high spinal block, as was noted in one patient (0.7%). GA always has a risk due to volatile or intravenous anaesthetics, ventilation and the longer duration of surgery. In addition, 7.5% of patients undergoing SA had to be converted to GA. Comparing our findings to others, we observed variation in the failure rate, ranging from 3%[40] to 15%.[17] Lambertz *et al*[31] emphasised the anaesthesiologist's experience as essential to ensure the maximum success rate. Overall, regarding these experiences performing spinal blocks for inguinal hernia repair, we conclude that SA is a safe method. Due to a lack of experience, it is associated with a lower success rate than GA, but it provides advantages by being technically simple and fast and limiting risks that require postoperative intervention.

Neurotoxicity was not discussed in any of the comparison studies. Patients were usually followed up until they left the hospital. Davidson *et al*[17] found no difference in neurodevelopment at the age of two between a sevoflurane group (of less than 1 hour exposure) and a group of patients who underwent regional anaesthesia. However, there is a major need for an investigation of the long-term effects.

The outcome parameters of postoperative ventilation and bradycardia changed to non-significant when we added the double-zero studies into our analysis. As double-zero studies do not add information to the decision regarding which treatment should be preferred, Cochrane recommends excluding these studies.[41] The relative risk estimates remained approximately the same. By including the double-zero studies, the differences between SA and GA could not be classified as significantly different as the CIs became very wide. We therefore recommend not overinterpreting the results of the analysis that included the double-zero studies.

To the best of our knowledge, no meta-analysis has considered trials focused only on comparing SA to GA for inguinal hernia repair in preterm-born neonates. When we looked at other large randomised studies that also compared SA to GA for other operations in infants, it was discovered that hypotension was more frequent in the GA group and that SA patients had shorter operation durations and hospital stays.[16 42 43] The regional anaesthesia methods (spinal, caudal and epidural) used were mixed in one large meta-analysis, which included studies of infants born preterm undergoing hernia repair and compared them with a GA group.[44] A strength of our review is that we excluded all studies with any other type of regional method to compare the possible advantages of the two methods. Additionally, we included the selected data from the largest study by Davidson *et al*.[17] For future investigations, we suggest a well-designed and adequately powered study with neonates born preterm who are still preterm while undergoing hernia repair, as most of the infants in our meta-analysis were not premature at the point of hernia fixation.

CONCLUSIONS

Our results suggest that SA is at least as safe as GA for inguinal hernia repair because it had an overall small failure rate and reduced the risk for any postoperative apnoea, bradycardias and the need for mechanical ventilation. Therefore, SA is a convenient alternative for hernia repair in infants born preterm. However, more RCTs with larger numbers of patients are needed to increase the quality of evidence.

Author affiliations
[1]Department of Anesthesiology, University Hospital RWTH Aachen, Medical Faculty, Aachen, Germany
[2]Department of Intensive Care Medicine, University Hospital RWTH Aachen, Medical Faculty, Aachen, Germany
[3]Department of Medical Statistics, Univeristy Hospital RWTH Aachen, Medical Faculty, Aachen, Germany

Acknowledgements Assistance with the study: We thank the GAS Consortium for the support with their data and the friendly exchange of information. We also thank Dr Risto Rintala, Dr Emily Harville and Dr Isabel Elaine Allen for their efforts and contributions in reviewing our meta-analysis.

Contributors GS and KD conceived of the study design of the review. GS and KD performed the literature search and eligibility assessment. KD performed the data extraction. GS and KD individually assessed the study quality and data analysis. TB reviewed the manuscript in terms of statistical methods analysis and structure. Clinical input and assistance with the discussion was given by GS, RR, CBE, MC, MH and CS. KD wrote the manuscript. All authors reviewed the manuscript and approved it.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iD
Katharina Dohms http://orcid.org/0000-0003-1835-4643

REFERENCES

1 Gray HT. A study of spinal anæsthesia in children and infants from a series of 200 cases. *The Lancet* 1909;174:991–6.
2 Lee JH, Zhang J, Wei L, *et al*. Neurodevelopmental implications of the general anesthesia in neonate and infants. *Exp Neurol* 2015;272:50–60.
3 McCann ME, de Graaff J. Current thinking regarding potential neurotoxicity of general anesthesia in infants. *Curr Opin Urol* 2017;27:27–33.
4 Gharavi-Fard M, Taghavi-Gilani M, Kazemi S, *et al*. Apneas in infants with postconceptional age bellow 60 weeks undergoing herniorrhaphy. *Iran J Pediatr* 2014;24:179–83.
5 Rozema T, Westgate PM, Landers CD. Apnea in preterm and term infants after deep sedation and general anesthesia. *Hosp Pediatr* 2018;8:314–20.
6 Laituri CA, Garey CL, Pieters BJ, *et al*. Overnight observation in former premature infants undergoing inguinal hernia repair. *J Pediatr Surg* 2012;47:217–20.
7 Wiener ES, Touloukian RJ, Rodgers BM, *et al*. Hernia survey of the section on surgery of the American Academy of pediatrics. *J Pediatr Surg* 1996;31:1166–9.
8 Chang S-J, Chen JY-C, Hsu C-K, *et al*. The incidence of inguinal hernia and associated risk factors of incarceration in pediatric inguinal hernia: a nation-wide longitudinal population-based study. *Hernia* 2016;20:559–63.
9 Krieger NR, Shochat SJ, McGowan V, *et al*. Early hernia repair in the premature infant: long-term follow-up. *J Pediatr Surg* 1994;29:978–82.
10 Lao OB, Fitzgibbons RJ, Cusick RA. Pediatric inguinal hernias, hydroceles, and undescended testicles. *Surg Clin North Am* 2012;92:487–504.
11 Philip AG. Neonatal mortality rate: is further improvement possible? *J Pediatr* 1995;126:427–33.
12 Costeloe KL, Hennessy EM, Haider S, *et al*. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ* 2012;345:e7976.
13 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8:336–41.
14 William JM, Stoddart PA, Williams SA, *et al*. Post-Operative recovery after inguinal herniotomy in ex-premature infants: comparison between sevoflurane and spinal anaesthesia. *Br J Anaesth* 2001;86:366–71.
15 Bouchut JC, Dubois R, Foussat C, *et al*. Evaluation of caudal anaesthesia performed in conscious ex-premature infants for inguinal herniotomies. *Paediatr Anaesth* 2001;11:55–8.
16 McCann ME, Withington DE, Arnup SJ, *et al*. Differences in blood pressure in infants after general anesthesia compared to awake regional anesthesia (GAS Study-A prospective randomized trial). *Anesth Analg* 2017;125:837–45.
17 Davidson AJ, Morton NS, Arnup SJ, *et al*. Apnea after awake regional and general anesthesia in infants: the general anesthesia compared to spinal anesthesia study--comparing apnea and neurodevelopmental outcomes, a randomized controlled trial. *Anesthesiology* 2015;123:38–54.
18 Frawley G, Bell G, Disma N, *et al*. Predictors of failure of awake regional anesthesia for neonatal hernia repair: data from the general anesthesia compared to spinal anesthesia study--comparing apnea and neurodevelopmental outcomes. *Anesthesiology* 2015;123:55–65.
19 Somri M, Gaitini L, Vaida S, *et al*. Postoperative outcome in high-risk infants undergoing herniorrhaphy: comparison between spinal and general anaesthesia. *Anaesthesia* 1998;53:762–6.
20 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
21 Schwarzer G, Carpenter JR, Rücker G. Small-study effects in meta-analysis. In: Schwarzer G, Carpenter JR, Rücker G, eds. *Meta-Analysis with R*. Cham: Springer, 2015: 107–41.
22 Schünemann H, Brożek J, Guyatt G, *et al*. 5. Quality of evidence. In: *GRADE Handbook for grading quality of e0vidence and strength of recommendations*, 2013.
23 Ryan R, Hill S. *How to GRADE the quality of the evidence*. London, UK: Cochrane Consumers and Communication Group, 2016.
24 Petitti DB. Approaches to heterogeneity in meta-analysis. *Stat Med* 2001;20:3625–33.
25 Berkey CS, Hoaglin DC, Mosteller F, *et al*. A random-effects regression model for meta-analysis. *Stat Med* 1995;14:395–411.
26 Higgins JPT, Green S. *Cochrane Handbook for systematic reviews of interventions version 5.1.0*. London, UK: The Cochrane Collaboration, 2011.
27 Gagnier JJ, Moher D, Boon H, *et al*. Investigating clinical heterogeneity in systematic reviews: a methodologic review of guidance in the literature. *BMC Med Res Methodol* 2012;12:111.
28 Deeks JJ, Julian PTH. *Statistical algorithms in review manager 5: on behalf of the statistical methods group of the Cochrane collaboration*. London, United Kingdom: The Cochrane Collaboration, 2010.
29 Kuss O. Statistical methods for meta-analyses including information from studies without any events-add nothing to nothing and succeed nevertheless. *Stat Med* 2015;34:1097–116.
30 Kim GS, Song JG, Gwak MS, *et al*. Postoperative outcome in formerly premature infants undergoing herniorrhaphy: comparison of spinal and general anesthesia. *J Korean Med Sci* 2003;18:691–5.
31 Lambertz A, Schälte G, Winter J, *et al*. Spinal anesthesia for inguinal hernia repair in infants: a feasible and safe method even in emergency cases. *Pediatr Surg Int* 2014;30:1069–73.
32 Krane EJ, Haberkern CM, Jacobson LE. Postoperative apnea, bradycardia, and oxygen desaturation in formerly premature infants: prospective comparison of spinal and general anesthesia. *Anesth Analg* 1995;80:7–13.
33 Welborn LG, Rice LJ, Hannallah RS, *et al*. Postoperative apnea in former preterm infants: prospective comparison of spinal and general anesthesia. *Anesthesiology* 1990;72:838–42.
34 Coté CJ, Zaslavsky A, Downes JJ, *et al*. Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis. *Anesthesiology* 1995;82:809–22.
35 Das B, Batra YK, Panda NB, *et al*. Analgesia in the immediate postoperative period in infants undergoing inguinal herniorrhaphy: a comparison between spinal and general anesthesia. *J Anaesthesiol Clin Pharmacol* 2005;21:137–42.
36 Özdemir T, Arıkan A. Postoperative apnea after inguinal hernia repair in formerly premature infants: impacts of gestational age, postconceptional age and comorbidities. *Pediatr Surg Int* 2013;29:801–4.
37 Shenkman Ze'ev, Erez I, Freud E, *et al*. Risk factors for spinal anesthesia in preterm infants undergoing inguinal hernia repair. *J Pediatr* 2012;88:222–6.
38 Eichenwald EC, Committee on Fetus and Newborn. Apnea of prematurity. *Pediatrics* 2016;137:e20153757.
39 Wilhelm TJ, Anemana S, Kyamanywa P, *et al*. Anaesthesia for elective inguinal hernia repair in rural Ghana - appeal for local anaesthesia in resource-poor countries. *Trop Doct* 2006;36:147–9.
40 Williams RK, Adams DC, Aladjem EV, *et al*. The safety and efficacy of spinal anesthesia for surgery in infants: the Vermont infant spinal registry. *Anesth Analg* 2006;102:67–71.
41 Higgins JPT, Deeks JJ, Altman DG. Rare events (including zero frequencies). In: *Cochrane Handbook for systematic reviews of interventions. version 5.1.0*, 2011. www.handbook-5-1.cochrane.org/chapter_16/16_9_rare_events_including_zero_frequencies.htm
42 Ing C, Sun LS, Friend AF, *et al*. Adverse events and resource utilization after spinal and general anesthesia in infants undergoing pyloromyotomy. *Reg Anesth Pain Med* 2016;41:532–7.
43 Whitaker EE, Wiemann BZ, DaJusta DG, *et al*. Spinal anesthesia for pediatric urological surgery: reducing the theoretic neurotoxic effects of general anesthesia. *J Pediatr Urol* 2017;13:396–400.
44 Jones LJ, Craven PD, Lakkundi A, *et al*. Regional (spinal, epidural, caudal) versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy in early infancy. *Cochrane Database Syst Rev* 2015;20.