Postoperative complications of hypospadias repair in patients receiving caudal block vs. non-caudal anesthesia: A meta-analysis

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Abstract

Introduction: We performed a meta-analysis of the current literature to assess the association of caudal block and postoperative complication rates following hypospadias repair.
Methods: A Systematic literature search was conducted on October 2017. Five reviewers independently screened, identified, and evaluated comparative studies assessing postoperative outcomes following hypospadias repair with and without caudal block. The incidence of post-surgical complications from each study was extracted for caudal block and control groups to generate the odds ratio (OR) and corresponding 95% confidence intervals (CI). Effect estimates were pooled using inverse-variance method with random-effects model. Subgroup analyses were performed according to study type and hypospadias severity.
Results: Nine studies (2096patients) of low- to moderate-quality were included for meta-analysis. Overall pooled effect estimates demonstrated increased occurrence of postoperative complication rates among patients with caudal block (OR 2.32; 95% CI 1.29–4.16). Subgroup analysis according to hypospadias severity revealed that a significant increased OR in complication rate was noted among proximal hypospadias (OR 3.55; 95% CI 1.80–7.01), but not distal hypospadias (OR 1.31; 95% CI 0.59–2.88).
Conclusions: Our meta-analysis of poor-quality evidence may have revealed a significant association between caudal block and postoperative complications following hypospadias repair. However, subgroup analysis demonstrated that hypospadias severity is important in determining complication rates, suggesting that confounding factors and selection bias may play a central role in characterizing the true effect of the anesthesia approach.

Introduction

Hypospadias repair is one of the most common urologic surgeries performed among pediatric population for congenital anomaly correction (1). To provide adequate intra- and postoperative analgesia during hypospadias repair, pediatric anesthesiologists more commonly consider giving caudal anesthesia than local blocks for its durability and good safety profile (2, 3, 4). However, several recent studies have identified caudal anesthesia as a risk factor for complications after hypospadias repair, such as urethrocutaneous fistula formation, glans dehiscence and meatal stenosis (4,5,6). On the contrary, some studies and commentaries have postulated that confounders such as the severity of the disease and not the type of anesthesia is the risk factor for the development of complications (7,8). Due to inconsistencies of study results, there is no clear evidence to indicate that caudal anesthesia increases the development of post-operative surgical complication in post-hypospadias repair. To address the aforementioned circumstances, we performed a meta-analysis of current literatures to assess the association of caudal anesthesia and postoperative complication rates following hypospadias repair.

Methods

The protocol of this review was registered with PROSPERO registry (CRD 42017079661). The study was preformed according to the Cochrane Collaboration recommendations and complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (9,10). The search strategy was developed in consultation with a health sciences librarian at McMaster University. The literature search was performed with no language restrictions on the following database from inception until October 30, 2017: MEDLINE, EMBASE, SCOPUS, Cochrane Library, including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL). Unpublished and ongoing trials were searched on Clinicaltrial.gov. Both medical subject heading (MeSH) and free text were used: ((hypospadias [MeSH Terms] OR hypospadias [All Fields]) OR urethroplasty[All Fields]) AND(caudal[All Fields] OR (anesthesia, caudal [MeSH Terms] OR ("anesthesia"[All Fields] AND "caudal"[All Fields]) OR "caudal anesthesia"[All Fields] OR ("anesthesia"[All Fields] AND "caudal";[All Fields]) OR "anesthesia, caudal"[All Fields])). The references from the reviews on the topic, textbooks of related topics and studies that met our inclusion criteria were reviewed and cross-referenced for possible eligible records to be considered for the meta-analysis.

Inclusion criteria for selection of the study were randomized/quasi-randomized controlled trials, prospective and retrospective comparative studies (both cohort and case-controlled studies) that assessed the outcome of post-operative complications in male pediatric patients who underwent hypospadias repair under caudal block and compared to other analgesia or no analgesia as control group. The primary outcome assessed in this review was the overall complication rate of all kinds of hypospadias surgery. Post-operative complications include urethrocutaneous fistula, meatal stenosis, diverticula, glans dehiscence and urinary retention were collectively treated as the composite primary outcome for this meta-analysis. No time restriction was placed on occurrence of post-operative complications from surgery. Studies or trials that did not state the complication outcomes stratified according to intervention groups were excluded since the effect estimate for the intervention cannot be assumed.

Five reviewers from two different institutions independently assessed the retrieved records and respective abstract according to the inclusion criteria. All records that were tagged by any of the reviewers were evaluated further for appropriateness and tagged for full-text retrieval. The evaluation and appraisal of the retrieved full-text articles were performed by two reviewers for final eligibility. Studies deemed eligible were assessed for methodological quality and risk of bias using the Cochrane Collaboration risk of bias tool, Newcastle-Ottawa quality assessment scale (NOQAS) and Risk of Bias in Non-Randomized studies- Intervention (ROBINS-I), for the randomized controlled trials and comparative studies (Cohorts and case-control studies), respectively (9,11). Discrepancies that arose in the assessment of individual studies were resolved by consensus or by the senior author. Data extraction from the included studies was done independently by two pairs of reviewers with cross validation. Raw data of event rate per group as reported from the individual studies were extracted for the extrapolation of odds ratio (OR) and 95% confidence intervals (CI). Intention-to-treat analysis was employed for the randomized studies if missing data was noted, and the assumption of missing data was done in favor of control. Whenever available, the adjusted effect estimates derived from multivariate analysis on the assessment of caudal anesthesia as independent predictor of post-hypospadias repair complication were likewise extracted and later pooled with other calculated OR and 95%CI. If same study cohorts or multiple publications were seen, only the most recent publication or the most complete data reported was included for meta-analysis.

To address likely presence of detectable and undetectable clinical and methodological variability of the studies included, all extracted study data were pooled using general inverse variance method with random effect model to generate an average effect estimate. Sensitivity analysis was likewise performed to assess for presence of heterogeneity using Chi square with two-sided α level of 0.10 was considered presence of significant heterogeneity. The inter-study variability was further estimated using the I^2 statistic, which indicates the proportion of total variation in estimates attributed to heterogeneity. A cut-off of 50% for I^2 was used to represent moderate heterogeneity, which is considered significant for variability that requires additional subgroup or sensitivity analysis to identify source of heterogeneity. Subgroup analyses were performed according to study type and hypospadias severity to confirm whether the priori subgroup analysis could lessen the heterogeneity. Once moderate inter-variability was still noted despite subgroup analyses, the source of heterogeneity was identified, and then a repeat meta-analysis was performed by excluding the study identified as the source of heterogeneity. Evaluation for presence or absence of publication bias was performed via visual inspection of funnel plot generated by RevMan5 software, which was also the same program for the calculation of the effect estimate of OR and corresponding 95%CI, while the Comprehensive meta-analysis software was used to conduct the meta-analysis for the pooled effect estimates of calculated OR and extracted adjusted OR and further statistical assessment of publication bias using Begg and Mazumdar rank correlation with Kendall's statistics (12, 13).

Results

The systematic literature search retrieved 502 records. Figure 1 summarizes the study selection process. After the duplicate records removed, out of the 189 records, 12 publications from 9 studies met the eligibility criteria for inclusion. Amongst the 9 studies, 7 were cohort design (5, 6, 7, 8, 14, 16, 17), one was a case-control (15), and one randomized controlled trial (4). All studies employed caudal anesthesia in at least one subgroup of patients and compared post-operative complications against other analgesics including dorsal penile block (n=5), continuous epidural analgesia (n=1), general anesthesia with no regional blockade (n=2), or IV anesthesia (n=1). The study characteristics of the included studies were summarized on Table 1.

Study quality

Using the NOQAS on the study quality screening of the comparative studies, scores ranging from 6 to 8 were noted. Further appraisal of the studies with ROBINS-I indicated moderate risk of bias for all cohorts and case control studies (Tables 2A–C). Confounding variables and selection of the reported result were accountable for the majority of the biases identified. These included severity of hypospadias, and presence of ventral curvature as factor of patient selective bias in group assignment. Additionally, majority of studies were retrospective in nature and several of these did not clearly outline their criteria for participant selection, which contributed to a lack of clarity when assessing selection bias or reporting bias as a result of the chosen subgroup. Cochrane Risk of bias assessment tool was used to evaluate the RCT, which showed moderate risk of bias (Tables 2A–C). Overall, the included studies were considered low to moderate quality evidence.

Effect of intervention

Overall, the nine studies included a total of 2,096 patients undergoing hypospadias repair. Of which, 1,225 patients received caudal anesthesia, and 871 under the comparator group. Among those received a caudal blockade, 171 (14%) patients developed post-operative complications, as compared to 53 (6.1%) patients in the comparator group. Extracted from the individual studies, the incidence of post-operative complications in caudal groups ranges from 3.7% to 37.5%; while 0% to 38.2% in non-caudal group. Overall pooled effect estimate extracted from the raw event rate from each intervention group showed significantly higher post-operative complications among the caudal anesthesia group (OR 2.32; 95% CI 1.29- 4.16) (Figure 2.1). However, a significant heterogeneity was noted on overall effect estimate pooling (Chi square= 17.11, p=0.03, I-squared= 53%). Subgroup analysis according to study type, noted a decreased inter-study variability among cohort studies (Chi square= 9.36, p=0.15, I squared= 36%) and sustained the significantly higher OR for caudal group (OR 2.59, 95%CI 1.49-4.51). When the adjusted effect estimates extracted from the multivariate analyses of the studies that reported them, the inter-study variability was lessened; however, still with evident heterogeneity noted (chi-square =15.86, p= 0.04, I^2= 50%). The overall pooled estimate with the adjusted OR remained in favor of the control groups (OR 2.27, 95%CI 1.29-4.01) (Figure 2.2).

Subgroup analysis

Further subgroup analysis according to hypospadias severity, showed that subgroup analysis for proximal hypospadias with no inter-study heterogeneity (chi-square=0.7, p= 0.71, I^2= 0%), sustained the findings of significantly higher occurrence of post-operative complications among the caudal anesthesia group (OR 3.55, 95%CI 1.8-7.01, p<0.001) (Figure 3). On the contrary, the subgroup analysis among distal hypospadias patients, no between group difference was noted (OR 1.31, 95%CI 0.6-2.88, p=0.50). However, heterogeneity with moderate inter-study variability was still noted (chi-square=10.5, p= 0.06, I^2=52.36%) (Figure 4.1). The study data from Zaidi 2015 was identified as source of heterogeneity, mainly due to its study type of case-control as compared to the other study type of cohorts. When this study was removed and repeat sensitivity analysis was performed, the heterogeneity was not evident (Chi squared=6.06, p=0.14, I squared=42%) and the pool effect estimate remained no significant difference between the intervention groups (OR 1.6, 95%CI 0.76- 3.43, p=0.21) (Figure 4.2).

Publication bias

Upon visual inspection of the funnel plot to determine the presence of publication bias, the plot of standard error by log odds ratio from the included studies was suggestive of publication bias (Supplementary Figure 1). Further statistical validation using Begg and Mazumdar rank correlation employing Kendall's statistics, confirms the presence of publication bias in reporting significant findings (Kendall's P-O= 20, Tau =0.56, z= 2.09, p=0.04).

Discussion

Currently, there exists much debate surrounding the use of different analgesics in hypospadias repair, in particular the caudal anesthesia raises a concern with the incidence of post-surgical complications. The finding from our meta-analysis of overall pooled effect estimates suggests that compared to control group, an increased occurrence of post-operative complications in hypospadias repair among who was given with caudal anesthesia (OR 2.27, 95%CI 1.29-4.01). Current literature has postulated that there may indeed be a association between the use of caudal analgesia in hypospadias surgery and development of complications including fistula, meatal stenosis, and glans dehiscence (18). Some data have supported that penile engorgement occurs during caudal anesthesia due to sympathetic block and vasodilation of the penile sinuses, causing venous pooling and resultant tissue edema (14). All together, these speculations on physiological changes caused by caudal anesthesia may have effect on surgical outcome has led to vast debate on its safety, risk and benefit for hypospadias repair. However, a clear underlying physiological mechanism is yet to be understood.

Some authors suggest that a higher incidence of postoperative edema may result to delayed wound healing, but this assumption has not been adequately tested (4, 8). Available clinical studies have not characterized the anesthetic intervention itself as independent factors contributing to the incidence of post-operative complications (7,8). Furthermore, there are many confounding factors that could affect the development of post-operative complications. Such that Zaidi et al (2015) have found that the use of epinephrine subcutaneously to control bleeding may play a role in inadequate tissue healing, which was further supported by Ayob et al 2016 in their investigative study that ischemic reperfusion injury can be the mechanism behind the fistula formation (8, 18).

It is important to note however, that our analysis revealed that the significant association between occurrences of post-operative complications in patients with caudal blockade was sustained with cohort studies of moderate risk of bias in methodological quality due to selection bias and confounding (OR 2.59, 95%CI 1.49- 4.51) and subgroup assessment of proximal hypospadias (OR 3.55, 95%CI 1.8-7.01), but not in patients with distal hypospadias (OR 1.31, 95%CI 0.6-2.88). This reinforces that hypospadias severity and other confounders are important intervening factors in considering the association between regional blockade and complications. Previous literature has identified that proximal hypospadias, a more severe phenotype of the condition, is linked to higher rates of complications post-operatively (19, 20). Likewise, the hypospadias severity is an important confounding variable to consider a subgroup analysis to actually identify the causality or correlation of an intervention (21). In the choice of anesthesia, the subpopulations of proximal hypospadias are more likely to be given with caudal anesthesia over other anesthesia approach due to its more complex repair and long duration procedure. Particularly evident in this review, the pooled number of patients within the proximal subgroup receiving caudal analgesia was more than double the size of the group not receiving caudal block. This is reflective of a clinical selection bias in which patients with more severe hypospadias are more likely to receive caudal analgesia. However, it is likewise important to consider that proximal hypospadias repair with extensive dissection plus the physiologic change from caudal anesthesia, could lead to an overall increased occurrence of surgical complications. Noting these findings, as a key role of the clinician is to minimize harms to the patient, this postulation brings into question a new element of surgical planning that may require attention for children undergoing hypospadias repair, specifically among proximal type cases (19).

It is acknowledged that this meta-analysis has some major limitations. Most notably, that despite comprehensive literature search using sensitive search strategies, the available literature on the topic is mainly comprised of uncontrolled comparative studies, which most of them were retrospective in nature. Although a randomized controlled trial was found, yet only a small number of patients were included in the study with some concern on the risk of bias, rendering it a low to moderate quality of evidence. Additionally, not all comparative studies included in this review have adequately controlled for confounding factors that may have influenced the true estimation of the association between caudal analgesia and postoperative complications. We mitigated this issue by using the adjusted point estimates whenever available from the included individual studies in pooling of effect estimates for the meta-analysis. Furthermore, we applied repeat sensitivity analysis with priori determined subgroup analysis to identify source of heterogeneity to minimize the effect of selection and confounding bias. Presence of publication bias in the available literature to generate the evidence was another considerable limitation. Base on GRADE criteria, the quality of evidence generated from our review, due to imprecision, inconsistency as well as publication bias, the body of evidence can only be considered at best a low quality to give any recommendations (22). Although, given such major limitation, the important message of our review is to increase cognizance that better-quality study should be made to generate more concrete evidence. Likewise, the review addresses a pertinent field of knowledge for healthcare practitioners to accurately characterize the association between caudal analgesia and post-operative complications of hypospadias repair. Lastly, our literature search has identified three ongoing randomized controlled trials, which are warranted to consider the confounders we discussed in this paper, while also expected to address the publication bias, if negative results would be noted.

Conclusion

The result of our meta-analysis revealed a significant association between caudal anesthesia and postoperative complications following hypospadias repair. However, subgroup analysis demonstrated that hypospadias severity is an important intervening factor that plays a role in determining complication rates associated with caudal anesthesia. The current available evidence was limited by its low quality suggesting that confounding factors and selection-bias may play a central role in characterizing the true effect of anesthesia type. A well-designed, adequately powered randomized controlled trial is warranted to confirm these findings.

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Figures and Tables

Fig. 1. PRISMA literature search and screening flow chart.

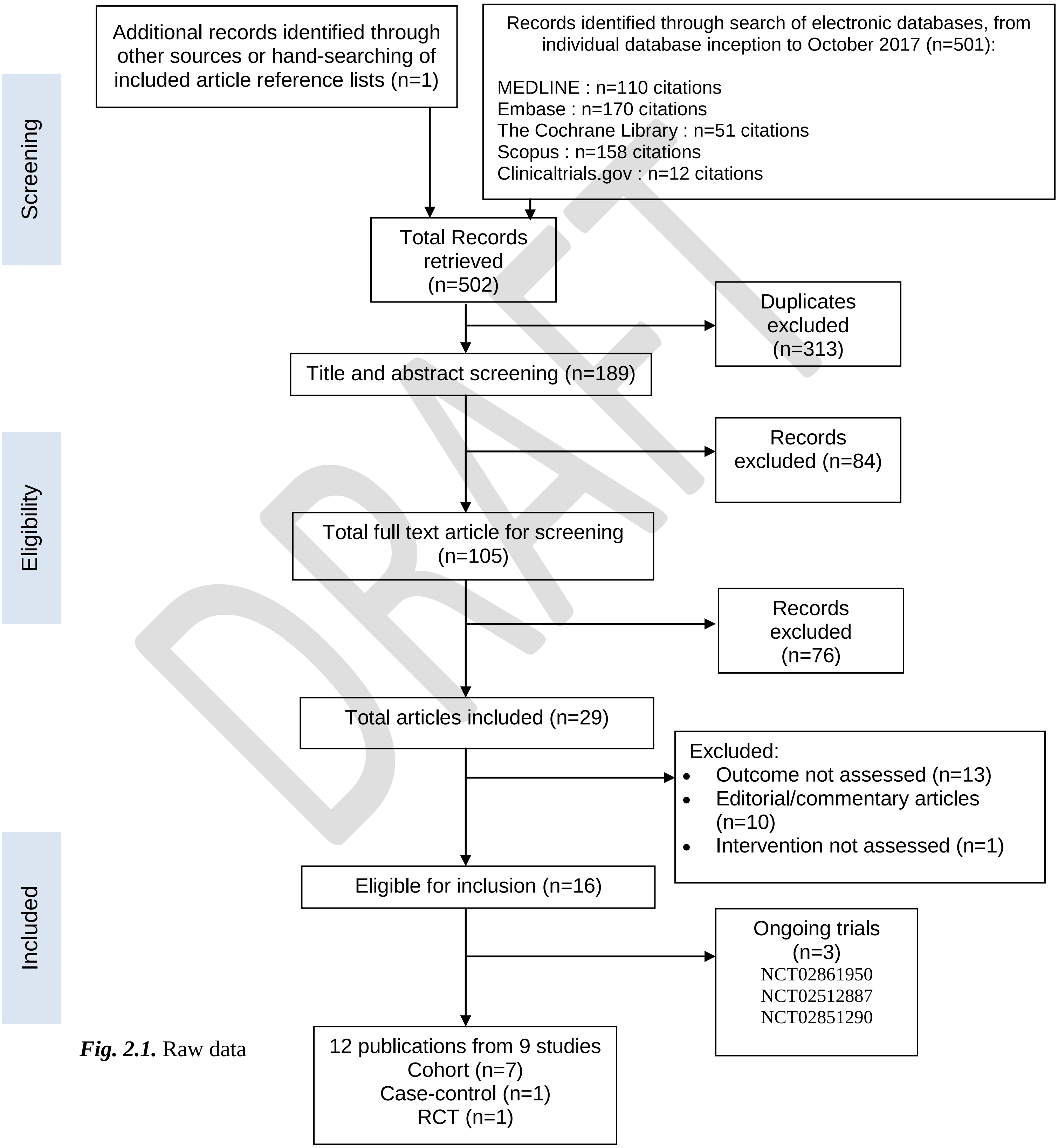


Fig. 2.1. Raw data

extracted for event per intervention group. Overall comparison: caudal anesthesia versus control group; outcome: postoperative complication; inverse-variance method with random-effect model. Subgroup according to study type. CI: confidence interval.

	Favours [Caudal]		Control			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year
2.1.1 Case Control							
Zaidi 2015	32	101	13	34	16.4%	0.75 [0.33, 1.68]	2015
Subtotal (95% CI)		**101**		**34**	**16.4%**	**0.75 [0.33, 1.68]**	
Total events	32		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.70 (P = 0.48)							
2.1.2 Cohorts							
Hakim 1996	5	136	6	200	11.8%	1.23 [0.37, 4.13]	1996
Ugras 2006	9	24	2	30	8.2%	8.40 [1.60, 43.98]	2006
Kim 2016	53	216	19	126	19.3%	1.83 [1.03, 3.26]	2016
Kreysing 2016	4	33	4	37	9.5%	1.14 [0.26, 4.96]	2016
Taicher 2017	21	230	1	165	6.2%	16.48 [2.19, 123.78]	2017
Braga 2017	32	367	5	151	14.5%	2.79 [1.07, 7.30]	2017
Saavedra-Belaunde 2017	10	91	3	101	10.7%	4.03 [1.07, 15.15]	2017
Subtotal (95% CI)		**1097**		**810**	**80.3%**	**2.59 [1.49, 4.51]**	
Total events	134		40				
Heterogeneity: Tau² = 0.19; Chi² = 9.36, df = 6 (P = 0.15); I² = 36%							
Test for overall effect: Z = 3.36 (P = 0.0008)							
2.1.3 Randomized Controlled Trials							
Kundra 2012	5	27	0	27	3.4%	13.44 [0.70, 256.40]	2012
Subtotal (95% CI)		**27**		**27**	**3.4%**	**13.44 [0.70, 256.40]**	
Total events	5		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.73 (P = 0.08)							
Total (95% CI)		**1225**		**871**	**100.0%**	**2.32 [1.29, 4.16]**	
Total events	171		53				
Heterogeneity: Tau² = 0.37; Chi² = 17.11, df = 8 (P = 0.03); I² = 53%							
Test for overall effect: Z = 2.82 (P = 0.005)							
Test for subgroup differences: Chi² = 7.95, df = 2 (P = 0.02), I² = 74.8%							

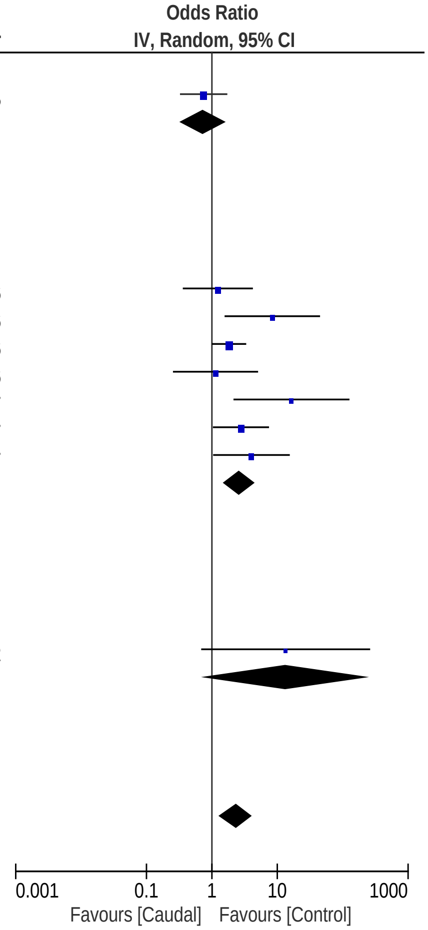


Fig. 2.2. Adjusted odds ratio and raw data extracted for event per intervention group. Overall comparison: caudal anesthesia versus control group; outcome: postoperative complication; inverse-variance method with random-effect model. CI: confidence interval.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Hakim 1996	1.230	0.368	4.109	0.336	0.737
Ugras 2006	8.400	1.602	44.040	2.518	0.012
Kundra 2012	13.440	0.702	257.223	1.725	0.084
Zaidi 2015	0.750	0.332	1.692	-0.693	0.488
Kim 2016	2.080	1.138	3.803	2.379	0.017
Kreysing 2016	1.140	0.261	4.979	0.174	0.862
Taicher 2017	13.400	1.782	100.773	2.521	0.012
Saavedra-Belaundre 2017	4.030	1.071	15.164	2.061	0.039
Braga 2017	2.390	0.892	6.404	1.733	0.083
OVERALL Effect estimates	2.269	1.285	4.007	2.825	0.005

Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
15.860	8	0.044	49.559	0.332	0.361	0.130	0.576

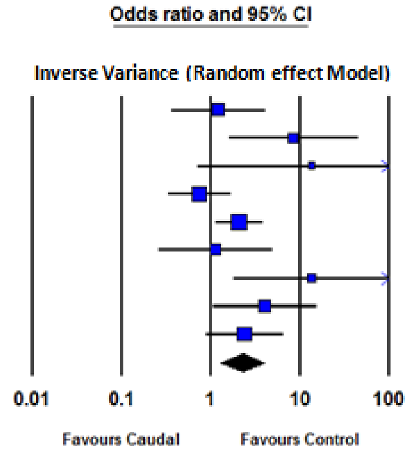


Fig. 3. Adjusted odds ratio and raw data extracted for event per intervention group. Subgroup analysis: proximal hypospadias; comparison: caudal anesthesia vs. control group; outcome: postoperative complication; inverse-variance method with random-effect model. CI: confidence interval.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Kim 2016	3.140	1.497	6.587	3.027	0.002
Braga 2017	6.160	0.742	51.144	1.684	0.092
Taicher 2017	8.250	0.472	144.160	1.446	0.148
OVERALL Effect estimates	3.554	1.802	7.010	3.659	0.000

Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
0.700	2	0.705	0.000	0.000	0.859	0.738	0.000

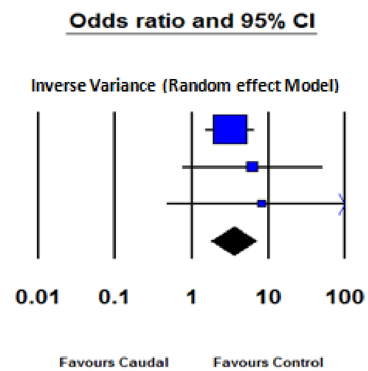
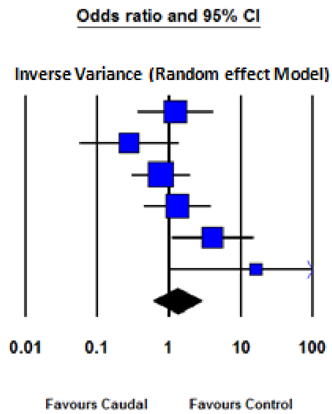


Fig. 4.1. Adjusted odds ratio and raw data extracted for event per intervention group. Subgroup analysis: distal hypospadias; comparison: caudal anesthesia vs. control group; outcome: postoperative complication; inverse-variance method with random-effect model. CI: confidence interval.

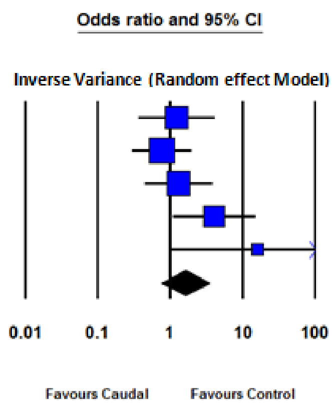
Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Hakim 1996	1.230	0.368	4.109	0.336	0.737
Zaidi 2015	0.280	0.057	1.376	-1.567	0.117
Kim 2016	0.770	0.299	1.983	-0.541	0.588
Braga 2017	1.310	0.448	3.827	0.494	0.622
Saavedra-Belaunde 2017	4.030	1.071	15.164	2.061	0.039
Taicher 2017	16.230	0.938	280.738	1.916	0.055
OVERALL Effect estimates	1.310	0.595	2.883	0.670	0.503



Heterogeneity				Tau-squared			
Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
10.497	5	0.062	52.365	0.482	0.601	0.361	0.694

Fig. 4.2. Adjusted odds ratio and raw data extracted for event per intervention group. Subgroup analysis: distal hypospadias; comparison: caudal anesthesia vs. control group; outcome: postoperative complication; inverse-variance method with random-effect model (Zaidi et al 2015 excluded). CI: confidence interval.

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Hakim 1996	1.230	0.368	4.109	0.336	0.737
Kim 2016	0.770	0.299	1.983	-0.541	0.588
Braga 2017	1.310	0.448	3.827	0.494	0.622
Saavedra-Belaunde 2017	4.030	1.071	15.164	2.061	0.039
Taicher 2017	16.230	0.938	280.738	1.916	0.055
OVERALL Effect estimates	1.618	0.763	3.430	1.256	0.209



Heterogeneity				Tau-squared			
Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
6.868	4	0.143	41.759	0.295	0.510	0.260	0.543

Table 1. General characteristics of nine included studies

Study	Study type	n	Mean followup	Surgical technique(s)	Single surgeon?	Intervention	Comparator group(s)	Outcome(s) assessed
Braga et al, 2017, Canada	Cohort	518	13 months	TIP urethroplasty	No	Caudal	DPB (bupivicaine 0.25% without epi)	Fistula, glans dehiscence
Hakim et al, 1996, U.S.	Cohort	336	Minimum 6 months	Mathieu repair	No	Caudal	DPB, continuous epidural	Fistula, meatal stenosis, meatal retraction
Kim et al, 2016, South Korea	Cohort	342	6 months	Tubularized incised plate urethroplasty	Yes	Caudal (ropivicaine 0.15–0.2% 1–1.5 mL/kg)	IV (fentanyl 0.05–0.1 ug/kg bolus + 0.2–0.4 ug/kg/h)	Fistula, meatal stenosis
Kreysing et al, 2016, Germany	Cohort	70	3.28 years	N/A	Yes	Caudal	No caudal *DPB (n=1)	Fistula, dehiscence, meatal stenosis, cyst
Kundra et al, 2012, India	Randomized trial	54	N/A	Snodgrass urethroplasty, snodgraft technique, asopa I urethroplasty, scrotal flap technique, preputial island flap, onlay patch urethroplasty, urethral	No	Caudal (14opivacaine 0.25%, 0.5 ml/kg)	DPB (14opivacaine 0.25%, 0.5 mg/kg)	Fistula

				advancement				
Saavedra-Belaunde et al, 2017, U.S.	Cohort	192	4 years	Tubularization of urethral plate ± plate incision	Yes	Caudal (15opivacaine 0.25%, 1 mL/kg)	DPB (15opivacaine 0.25%)	Fistula, glans dehiscence, meatal stenosis
Taicher et al, 2017, U.S.	Cohort	395	Minimum 6 months	Hypospadias repair with Dartos flap	Yes	Caudal (15opivacaine 0.25% or 15opivacaine 0.12%)	DPB (15opivacaine 0.25% or 15opivacaine 0.12%)	Fistula, glans dehiscence
Ugras et al, 2006, Turkey	Cohort	54	N/A	Tubularized incised plate urethroplasty, Mathieu repair	No	Caudal	GA	Fistula, glans dehiscence
Zaidi et al, 2015, U.S.	Case control	135	Minimum 6 months	Tubularized incised plate urethroplasty, meatal advancement and glanuloplasty, preputial island onlay	No	Caudal	DPB	Fistula

Table 2A. Risk of bias assessment using the ROBINS-I tool for cohorts and case-control study								
	ROBINS-I							
Cohort study	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in measurement of interventions**	**Bias due to departures from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall bias**
Braga et al, 2017	Low	Moderate	Low	Low	Low	Moderate	Low	Moderate
Hakim et al, 1996	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Kim et al, 2016	Low	Moderate	Low	Low	Low	Low	Moderate	Moderate
Kreysing et al, 2016	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Saavedra-Belaunde et al, 2017	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Taicher et al, 2017	Low	Low	Low	Low	Low	Moderate	Moderate	Moderate
Ugras et al, 2006	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Case-control	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in measurement of interventions**	**Bias due to departures from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall bias**

Zaidi et al, 2015	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate

Table 2B. Risk of bias assessment using the Newcastle-Ottawa quality scale and case-control study									
NOQAS									
	Representativeness of the exposed cohort	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability**	**Assessment of outcome**	**Was followup long enough for outcomes to occur**	**Adequacy of followup of cohorts**	**Total NOS score**
Braga et al, 2017	1	1	1	1	2	1	x	1	8
Hakim et al, 1996	1	1	1	1	1	x	x	1	6
Kim et al, 2016	1	1	1	1	2	x	x	1	7
Kreysing et al, 2016	1	1	1	1	1	1	1	x	7
Saavedra-Belaun	1	x	1	1	1	1	1	x	6

de et al, 2017									
Taicher et al, 2017	1	1	1	1	1	1	x	1	7
Ugras et al, 2006	1	1	1	1	1	1	x	1	7
Case-control	**Case definition adequate**	**Representativeness of case**	**Selection of controls**	**Definition of control**	**Comparability**	**Ascertainment of exposure**	**Same method of ascertainment**	**Non-response rate**	**Total NOQAS**
Zaidi et al, 2015	1	x	1	x	2	1	1	1	7

Table 2B. Risk of bias assessment using the risk of bias for randomized controlled trial

Randomized controlled trial	Sequence generation	Allocation concealment	Blinding of participants	Blinding of assessors	Incomplete outcome data	Selective outcome reporting	Conflict of interest	Informed consent	Ethics board review	ITT	Other bias	Overall assessment
Kundra, 2012	Low	Low	High	Low	High	Unclear	Low	Low	Low	High	High	Low to mod

Supplementary Fig. 1. Funnel plot of standard error by log odds ratio from the included studies in the overall meta-analysis.