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Effects of General Anesthesia vs Regional Anesthesia on Neonatal Outcomes: A Systemic Review and Mata Analysis

Research Article

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Abstract

Backgrounds: Types of anesthesia provision and perioperative patient cares are the main determinants of neonatal outcome in mothers undergo caesarean section. Body of evidence didn't clearly reveal which types of Anesthesia technique is associated with better neonatal outcomes in mothers who gave birth under spinal anesthesia than general anesthesia. The aim of this systemic review and meta-analysis was to compare neonatal outcomes in mothers who undergo caesarean section under general anesthesia and regional anesthesia.

Methods: We carried out a systemic search of the electronic databases of central, Medline, Embase, LILACS, AOLJ and others with PICO strategy for controlled clinical trials comparing neonatal outcomes under general and regional anesthesia. Twenty trials were identified for eligibility assessment, ten trials were selected for data extraction, and nine trials were finally included in the meta-analysis. All controlled clinical trials using regional and general anesthesia for ASA I-II term pregnant women coming for cesarean section in elective and semi-urgent condition were selected. Eligibility assessment was performed independently by the two review authors using a customized form, while discrepancies were resolved by consensus. The Data from individual trial were extracted and entered Review Manager for synthesis.

Results: Ten studies (782 participants) were included in this review. The Apgar score at one minute less than seven was better in spinal anesthesia as compared to General Anesthesia (OR=0.24, 95% confidence interval (CI) 0.14 to 0.42, 5 trials, 548 participants). There was no significant association at 5th minute Apgar score less than seven (OR=-0.02, 95% CI -0.09 to 0.05, 3 trials, 260 participants). There was significant mean difference between spinal and general anesthesia on neonatal mean Apgar score at 5th minute (MD=0.51, 95% CI 0.14 to 0.88, 5 trials, 671 participants).

There was a significant mean difference on Umbilical artery and Venous PH when general anesthesia is compared with spinal anesthesia (MD= -0.01, 95% CI -0.002 top -0.00, one trial, 40 participants) and (MD= -0.98, 95% CI -1.66 to -0.30, one trial, 40 participants).

Conclusion: Regional Anesthesia is superior over general Anesthesia in certain neonatal outcomes as depicted by the pooled analysis of individual trials. However, there should be further review with individual trials having high power and similar dosage and techniques as most of the individual trials in this review are low powered and different types of outcome assessment techniques.

Keywords: Anesthesia; Apgar Score; Umbilical Artery PH; Umbilical Vein PH; Controlled Clinical Trial.

Abbreviations: AOLJ: African on Line Journal; BMI: Body Mass Index; CI: Confidence Interval; CMA: Comprehensive Meta-Analysis; ENNS: Early Neonatal Neurologic Score; ICU: Intensive Care Unit; LILACS: literature In Health Science In Latin America and Caribbean; MN: Mean Deviation; NACS: Neurologic Adaptive Capacity Score; OR: Odd Ratio; Revman: Review Manager; RR: Relative Risk; SD: Standard Deviation; SMD: Standardized Mean Difference.

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Background

Obstetric Anesthesia is a demanding but challenging subspecialty of anesthesiology and it requires special skills because two lives are involved at the same time at any time of the day. The choice of Anesthesia, either general or regional Anesthesia, for cesarean section depends upon indication for operation, its urgency, and preference of patients, obstetrician and anesthetist [1, 2]. Both general and spinal Anesthesia are not ideal for cesarean section because each has advantages and risk to fetus. However, the plan of anesthetist is to choose the method which is safest and most comfortable for the mother, least depressant to the newborn and which provides optimal working conditions for the obstetrician [2-4].

Spinal anesthesia affects neonates either by decreasing uteroplacental perfusion secondary to sympathetic blocked induced hypotension or intratecally administered Opioids with local anesthetics that depress the respiratory center and end up with asphyxia and acidosis [3, 4].

The effect of general anesthesia on neonate depends on intravenous agent, dosage of the agent and the total induction delivery time [1, 5].

According to a study conducted in India, the higher the induction delivery time the lower the Apgar score was in general anesthesia than regional anesthesia and the mean Early neonatal neurobehavioral score was higher in spinal (30 ± 1.3), general (28.3 ± 1.76 and epidural (28.4 ± 1.93) respectively [5].

The effect of types of Anesthesia on neonatal outcomes is uncertain that some studies showed no difference in neonatal outcomes between regional and general Anesthesia [6, 7] and others showed that neonatal outcomes are better in regional Anesthesia than general Anesthesia [3-5, 8-20].

It is very important to know the types of Anesthesia with better neonatal outcomes despite the risks and benefits of each type of Anesthesia.

Objective

To compare effects of General Anesthesia and Regional Anesthesia on Neonatal outcomes.

Criteria for Considering Studies for this Review

Types of study

Randomized controlled trials.

Types of participants

ASA I and II full term pregnant women with no fetal distress and abnormality coming for elective or emergency cesarean section.

Types of intervention

Intervention: Babies delivered with cesarean section under regional Anesthesia (spinal, epidural or combined spinal-epidural).

Control: Babies delivered with cesarean section under General Anesthesia.

Types of Outcomes

Primary outcomes: The primary outcomes were Apgar score at first and fifth minute less than seven, Apgar score at first and fifth minute greater than seven, mean Apgar score at first and fifth minute and umbilical blood gas analysis.

Secondary outcomes: The secondary outcomes were Neurobehavioral Adaptive capacity Score, need for resuscitation, hypoglycemia and phototherapy.

Search methods for identification of studies for the review

Ethical clearance was obtained from Dilla University research and dissemination office. We carried out a systemic search of the electronic database: central, Medline, Embase, LILACS, AOLJ and others with PICO strategy as described in methodology.

The search was restricted to full reports of randomized controlled trials published in peer-reviewed journals without excluding trials published in languages other than English and no date restriction was applied up to April 2015. Trials studying ASA I and II mothers with no fetal distress coming for elective or emergency caesarean section were incorporated in the Meta analysis.

Eligibility assessment was performed independently by the two review authors using a customized form, while discrepancies were resolved by consensus. Two Authors independently assessed each trial for inclusion in the review using the information described in the section 'Criteria for considering studies for this review' and Studies that did not meet the inclusion criteria were excluded and the reason was stated in the table of 'Characteristics of excluded studies' (Table 2).

We prepared a flow diagram to summarize the study selection process according to PRISMA chart.

As it has been mentioned in methodology, the two Authors searched independently the five major databases and some others. Trials identified through the search were given a code depending on the topic. We searched the database for potential eligibility studies without year and language restriction with medical subject heading (MeSH) terms of Neonate, Apgar, outcome, umbilical blood gas, Neonatal Adaptive capacity score and Ph as follows:

- 1. general
- 2. regional
- 3. spinal
- 4. epidural
- 5. #1 and (#2 or #3 or #4)
- 6. Anesthesia*
- 7. #5 and #6
- 8. cesarean section*
- 9. #8 and #9
- 10. random*
- 11. controlled-clinical-trial

PRISMA Flow Chart



12. #12 or #13 13. #11 and #14

Methods of the review

Semagn Mekonnen (SM) selected potentially relevant trials from those identified by the search strategy and retrieved the full articles and multiple publications from the same data set were only used once. SM and Siraji Ahmed (SA) independently assessed each trial for inclusion in the review using the information described in the section Criteria for considering studies for this review. Studies that did not meet the inclusion criteria were excluded and the reasons were stated in the table of Characteristics of excluded studies. SM and SA independently assessed the methodological quality of the included trials which were measured by Generation of allocation sequence, allocation concealment, blinding and loss to follow up. For all trials, each quality component apart from blinding were classed as adequate, inadequate or unclear, (Table 1). For allocation concealment, the letters A to D were used: where A =adequate, B = unclear, C = inadequate and D = not used. For loss to follow up, inclusion of 90% of participants was considered adequate. Blinding was assessed using the following criteria: blinding of participants, blinding of Health care providers and blinding of outcome assessment. Blinding was assessed as open or single blind. Disagreements between Authors were resolved by discussion.

Statistical combination of data from two or more separate trials in a meta-analysis was decided based on the evaluation of the clinical and methodological heterogeneity. The inconsistency throughout trials were quantified with the I² statistic proposed by Higgins and colleagues, assuming a value more than 50% as a substantial heterogeneity.

The summary effect measure were risk ratio (RR) and odd ratio for dichotomous variables and mean Difference and standard deviation for continuous variables along with their corresponding 95% confidence intervals (CI). The meta-analysis was planned to be performed through a random-effects model and Mantel– Haenszel (M–H) statistical method, anticipating that trials would have different techniques and assuming that the actual true effects have a normal distribution.

The data Analysis was conducted using Review Manager (RevMan 5.3, Cochrane Collaboration) and Comprehensive Meta-Analysis (CMA). This systematic review was carried out using the methods established by the Cochrane Handbook for Systematic Reviews of Interventions and we followed the recommendations and checklist items from the PRISMA Statement for Reporting Systematic Reviews and Meta-analysis.

Description of studies

The search strategies identified 300 trials from different data bases as mentioned in the methodology section (Figure 1). After a process of successive screening for eligibility, 20 studies were selected for more detail evaluation. With subsequent screening, 10 studies with 782 participants were included for analysis and the rest were excluded with reasons (Table 3).

The 10 studies analyzed were published between 1985- 2014 and they were performed in South America, Europe and Asia. The mean age of included studies ranged from 27-31years. Whereas the mean weight reported was 61-74 kg in four studies. The BMI of included studies was reported in four studies which were ranged from 25.4-29kg/m². Sample size ranged from 52-188 participants and only two studies had large sample size of 160 and 188. In six studies the neonatal outcomes were compared with General and spinal Anesthesia where as general, spinal and epidural anesthesia was compared for neonatal outcomes in three studies. Only one study compared neonatal outcomes with General and epidural Anesthesia.

General Anesthesia was induced with 4-6mg/kg thiopental and 1.5-2mg/kg succinylcholine in nine studies. Only one study was performed with propofol intravenous agent. Spinal Anesthesia was conducted with 0.5%-0.75% bupivacaine. The details were described in tables of excluded studies (Table 3).

Table 1. Description of included studies. GA: general Anesthesia; SA: spinal Anesthesia; Ep: epidural Anesthesia; * Spinal alone; Thio: thiopental; Bupi: bupivacaine; Fent: fentanyl; succ: succinylcholine; UA: umbilical Artery; UV: Umbilical vein; NACS: neurologic Adaptive Capacity Scores,** epidural Alone.

Study groups	sample (n)	county	GA groups	SA and or EP groups	outcome variables
Arif Yeuun and Colleagues	62	Turkey	5mg/kg thio 1.5mg:kg succ	EP: 15m1 of 0.5% bupi**	Apgar score, UA, UV
Kosam Durga and Colleagues	60	India	thio 4-5mg/kg +2mg/kg succ SA: 0.5% of 2.2- 2.5 ml bupi	EP: 12m1 of 0.5% bupi	Apgar score, UA, UV, NACS
Akyol A and Colleagues	62	Holland	5mg/kg thio + 1.5mg/kg succ	0.5% of 1.6 ml bupi and 20μg fent*	Apgar scores, UA, UV
Aftab Imtiaz and Colleagues	30	Pakistan	thio 4-5mg/kg +1.5mg/kg succ	0.5% of 3 ml bupi	Apgar scores, UA, UV
Saeed Ahmed and col- leadgues	160	pakistan	propofol 2mgrkg + 1.5mg/ kg succ	0.5% of 1.5 ml bupi	Apgar scores, UA, UV
Saleem Sabbar and Colleagues	100	Pakistan	not described	0.5% of 1.5 ml bupi	Apgar scores
Anil Ice and Colleagues	100	turkey	thio 4-5mglIcg +1.5mg,:kg suc	0.5% of 2.2 ml bupi*	Apgar scores, NICU
Rumina and Colleagues	100	Pakistan	not described	1.5m1 bupi*	Apgar scores
ABBOUD TK and	52	USA	thio 4-5mg/kg +1.5mtkg succ	0.5% of 2.2 ml bupi*	Apgar scores, UA, UV, NACS
Kolatat T and	341	Thailand	thio 4-5mg/kg +1.5mg/kg succ	0.5% of 2.2 ml bupi*	Apgar scores, U.A, UV, NACS

Table 2. Risk of Bias within studies. A: low risk; B: High risk; C: uncertain/unclear risk of bias. Jadal scale.

	sequence	allocation		incomplete	selective	free of		Jadal	
Study Scale	generation	concealment	blinding	outcome data	outcome Reporting	their bias	randamization	blinding	withdrawal
Arif Yeuun and Colleague	А	С	С	А	А	А	1	1	0
Kosam Durga and Colleagues	А	А	С	А	А	А	2	1	0
Akyol A and Col- leagues	А	С	С	А	А	А	1	1	0
Aftab Imtiaz and Colleagues	А	С	С	С	С	А	1	1	0
Saeed Ahmed and colleadgues	А	А	С	А	А	А	2	1	0
Saleem Sabbar and Colleagues	А	С	С	А	А	А	2	1	0
Anıl İçel and Col- leagues	А	С	С	А	А	А	1	1	0
Rumina and Col- leagues	А	С	С	А	А	С	1	1	0
ABBOUD TK and Colleagues	С	С	С	А	А	В	1	1	0
Kolatat T and Col- leagues	А	С	А	А	А	А	2	2	0

Tables 3. Characteristics of excluded studies.

Study	Reason for exclusion
MUHAMMAD A. 2004	Randomization was not done and mothers were with severe preeclampsia
Moslemi F. 2007	Randomization was not done and mothers were with severe preeclampsia
Shusee V. 2005	Randomization was not done and mothers were with severe preeclampsia
Suman C. 2013	Randomization was not done and mothers were with severe preeclampsia
Jawad Zahir 2011	Randomization was not done; study not controlled trial (cohort study design)
Charles S 2009	Randomization was not done; study not controlled trial (cohort study design)
TC Martin 2007	Randomization was not done; study not controlled trial (cohort study design)
G. Tonni 2006	Randomization was not done; study not controlled trial (cohort study design)
Sousan Rasooli 2013	Randomization was not done; study not controlled trial (cohort study design)

Results

Primary outcomes

The immediate outcomes of neonates were assessed with Apgar score and umbilical blood gas analysis and that was why the included studies primary outcomes were Apgar score and Umbilical blood gas analysis results. The 10 included studies reported the 1st and 5th minute Apgar scores and of which five studies [3, 5, 8-10] reported as mean \pm SD whereas the rest five reported as range of values. Neonatal umbilical blood gas was reported in five studies [4, 6, 7, 9, 11]. In six studies [3, 4, 8, 10, 11, 14] the first minute Apgar score is better in spinal anesthesia than general anesthesia whereas there were no significant different in the first minute Apgar score in two studies [6, 7] in whichever type of Anesthesia, general vs regional (spinal and epidural). In only one study [4], the Fifth minute Apgar score was better in spinal anesthesia whereas there were no difference in nine studies on the fifth minute Apgar score. The umbilical blood gas analysis were not significantly different in three studies [4, 10, 14] under general

and spinal anesthesia. However, the blood gas analysis were better in regional anesthesia than general anesthesia in two studies [6, 7].

Secondary outcomes

Neonatal neurobehavioral response: The neonatal neurobehavioral response was reported in three studies with different assessment tools. Two studies reported neonatal neurobehavioral response with neonatal adaptive capacity score [10, 11] which was measured at 15minute, 2hrs and 24hrs and babies delivered under general anesthesia had lower NACS as compared to Epidural and spinal groups but there were no difference at 24hrs where as one study reported with Early Neonatal Neurobehavioral Score [5].

Neonatal ICU Admission: Neonatal ICU admission was reported only in one study [9]. The numbers of neonates admitted to Neonatal ICU were higher in spinal 6(12%) as compared to general anesthesia which was 5 (10%) neonates.

Figure 1. Forest plot for Apgar score at 1 minute <7 comparing SA VS GA: individual trials and Meta-analysis. Events, the total numbers with the events total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. M–H, Mantel–Haenszel methods.

	opine	ai	Ochich	ai -		Ouus Nalio		Ouus			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	dom, 95% Cl		
Fadil HAVAS, 2013	0	95	3	93	3.6%	0.14 [0.01, 2.66]	(•			
Kosam Durga 2014	0	20	3	20	3.5%	0.12 [0.01, 2.53]	←				
Anıl İçel 2011	0	50	4	50	3.7%	0.10 [0.01, 1.95]	←	•	+		
Saleem Sabbar 2009	18	80	36	80	68.0%	0.35 [0.18, 0.70]					
Aftab Imtiaz, 2009	10	30	25	30	21.3%	0.10 [0.03, 0.34]					
Total (95% CI)		275		273	100.0%	0.24 [0.14, 0.42]		•			
Total events	28		71								
Heterogeneity: Tau ² = 0.0)0; Chi² = 3	3.89, di	f = 4 (P = ().42);	² = 0%					+	40/
Test for overall effect: 7 :	= 4.94 (P <	0 0 0 0 0)1)				0.01	U.1	1	IU 	100

Figure 2. Forest plot for Apgar score at 5 minute <7 comparing SA VS GA: individual trials and Meta analysis. Events, the total numbers with the events total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. M–H, Mantel–Haenszel methods.

	Spina	al	Gener	ral		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Kosam Durga 2014	0	20	0	20	29.0%	0.00 [-0.09, 0.09]	-+-
Saleem Sabbar 2009	0	80	6	80	40.4%	-0.07 [-0.14, -0.01]	
Aftab Imtiaz, 2009	30	30	29	30	30.6%	0.03 [-0.05, 0.12]	
Total (95% CI)		130		130	100.0%	-0.02 [-0.09, 0.05]	•
Total events	30		35				
Heterogeneity: Tau ² = 0.0	00; Chi ² = 4	4.60, d	f = 2 (P =	0.10);	² = 57%		
Test for overall effect: Z =	= 0.57 (P =	: 0.57)	·				-1 -0.5 U 0.5 Favours Spinal Anesthesia Favours General Anesthesi

Figure 3. Forest plot for Apgar score at 1 minute >7 comparing SA VS GA: individual trials and Meta-analysis. Events, the total numbers with the events total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. M–H, Mantel–Haenszel methods.

	Spina	al	Gene	ral		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Kosam Durga 2014	0	20	17	20	17.3%	0.03 [0.00, 0.44] 🔶	
Saleem Sabbar 2009	78	80	60	80	44.1%	1.30 [1.14, 1.48]	•
Aftab Imtiaz, 2009	20	30	5	30	38.6%	4.00 [1.73, 9.26]	
Total (95% CI)		130		130	100.0%	1.04 [0.24, 4.48]	
Total events	98		82				
Heterogeneity: Tau ² = 1.2 Test for overall effect: Z =	26; Chi² = = 0.05 (P =	16.69, (: 0.96)	df = 2 (P :	= 0.000	2); ² = 88	% 	01 0.1 1 10 100 Favours Spinal anesthesia Favours general anesthesi

Figure 4. Forest plot for Apgar score at 5 minute >7 comparing SA VS GA: individual trials and Meta-analysis. Events, the total numbers with the events total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. M–H, Mantel–Haenszel methods.



Figure 5. Forest plot for mean Apgar score at 1 minute comparing SA VS GA: individual trials and Meta-analysis. Total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: inverse variance.

		Spinal		G	ieneral			Mean Difference		Mean D	Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl		IV, Rand	lom, 95% Cl		
Fadıl HAVAS, 2013	7.21	0.16	95	7.1	0.92	93	20.5%	0.11 [-0.08, 0.30]			•		
Kolatat T, 1999	6.7	2.8	118	9.7	0.9	103	19.4%	-3.00 [-3.53, -2.47]			•		
Kosam Durga 2014	8.35	0.745	20	7	1.025	20	19.4%	1.35 [0.79, 1.91]			•		
Saleem Sabbar 2009	8.04	0.82	80	7.1	0.92	80	20.4%	0.94 [0.67, 1.21]			•		
Akyol A 2005	8.03	0.6	30	7.88	0.6	32	20.3%	0.15 [-0.15, 0.45]			•		
Total (95% CI)			343			328	100.0%	-0.08 [-1.03, 0.88]					
Heterogeneity: Tau ² = 1.	15; Chi²	= 184.0	9, df = 4	4 (P < 0	.00001)	; ² = 98	3%		-100	-50	0	50	100
Test for overall effect: Z	= 0.16 (F	9 = 0.87)							Favours Spinal Anesthesia	Favours Ger	eral Anesthesi	

Figure 6. Forest plot for mean Apgar score at 5 minute comparing SA VS GA: individual trials and Meta-analysis. Total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled Sample size of the meta-analysis. IR: inverse variance.

	ļ	Spinal		G	eneral			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	IV, Random, 95% CI
Fadıl HAVAS, 2013	7.344	0.051	95	7.327	0.045	93	23.2%	0.02 [0.00, 0.03]	+
Kolatat T, 1999	9.7	0.9	118	9.2	1.6	103	19.2%	0.50 [0.15, 0.85]	•
Kosam Durga 2014	8.35	0.745	20	7	1.025	20	15.2%	1.35 [0.79, 1.91]	•
Saleem Sabbar 2009	9.89	0.32	80	9.34	1.07	80	21.1%	0.55 [0.31, 0.79]	•
Akyol A 2005	7.98	0.5	30	7.56	0.4	32	21.3%	0.42 [0.19, 0.65]	
Total (95% CI)			343			328	100.0%	0.51 [0.14, 0.88]	
Heterogeneity: Tau ² = 0. Test for overall effect: Z	15; Chi² : = 2.72 (P	= 59.44 9 = 0.00	, df = 4 7)	(P < 0.0)0001);	² = 939	6		-100 -50 0 50 100 Favours Spinal Anesthesia Favours General Anesthesi

Figure 7. Forest plot for mean Apgar score at 1 minute comparing EA VS GA: individual trials and Meta-analysis. Total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: inverse variance.

	Epidura	al Anesth	iesia	Genera	l Anesth	esia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Arif Yeuun 2003	7.38	0	31	7.19	0.7	31		Not estimable	
Kolatat T, 1999	8.3	1.9	120	9.7	0.9	103	50.3%	-1.40 [-1.78, -1.02]	•
Kosam Durga 2014	8.35	0.745	20	7	1.025	20	49.7%	1.35 [0.79, 1.91]	
Total (95% CI)			171			154	100.0%	-0.03 [-2.73, 2.66]	•
Heterogeneity: Tau ² = Test for overall effect:	3.72; Chi² Z = 0.02 (F	= 63.96, P = 0.98)	df = 1 (P	< 0.0000	1); ² = 98	3%			-100 -50 0 50 100 Favours Epidural Anesthes Favours General Anesthesi

Figure 8. Forest plot for mean Apgar score at 5th minute comparing EA VS GA: individual trials and Meta-analysis. Total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: inverse variance.

	Epidura	l Anesth	esia	General	Anesth	esia		Mean Difference		Ν	lean Difference)	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV	, Random, 95%	CI	
Arif Yeuun 2003	9.87	0.42	31	9.54	0.67	31	50.7%	0.33 [0.05, 0.61]					
Kolatat T, 1999	8.2	1.6	120	9.2	1.6	103	49.3%	-1.00 [-1.42, -0.58]			•		
Total (95% CI)			151			134	100.0%	-0.33 [-1.63, 0.98]					
Heterogeneity: Tau ² = Test for overall effect: 2	0.85; Chi² = Z = 0.49 (P	= 26.66, (= 0.62))f = 1 (P	< 0.00001	l); ² = 96	6%			-100 Fav	-50 vours Epidural Ane	0 esthes Favour	50 50 s General Anesthe	

Figure 9. Forest plot for mean neonatal P0₂ comparing SA VS GA: individual trials and Meta analysis. Total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: inverse variance.

	(Spinal		Ģ	General		9	Std. Mean Difference		Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% Cl	
Fadıl HAVAS, 2013	28.1	8.8	95	38.1	15	93	17.7%	-0.81 [-1.11, -0.51]		•	
Kolatat T, 1999	9.7	0.9	118	9.2	1.6	103	17.8%	0.39 [0.12, 0.66]		+	
Kosam Durga 2014	8.35	0.745	20	7	1.025	20	15.0%	1.48 [0.77, 2.18]		•	
Saleem Sabbar 2009	9.89	0.32	80	9.34	1.07	80	17.6%	0.69 [0.37, 1.01]		•	
Akyol A 2005	7.309	0.02	30	7.308	0.02	32	16.6%	0.05 [-0.45, 0.55]		+	
ABBOUD TK, 1985	7.32	0.01	18	7.33	0.01	20	15.3%	-0.98 [-1.66, -0.30]		1	
Total (95% CI)			361			348	100.0%	0.13 [-0.51, 0.77]			
Heterogeneity: Tau ² = 0. Test for overall effect: Z	58; Chi² : = 0.39 (P	= 78.20 = 0.69	, df = 5)	(P < 0.(00001);	² = 940	6		-100	-50 0 50	100

Figure 10. Forest plot for mean neonatal Umblical Artery PH comparing SA VS GA: individual trials and Meta-analysis. Total: the total number of participants in intervention (SA) and control (GA). Weight: Sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: inverse variance.



Figure 11. Forest plot for mean ENNS comparing SA VS GA: individual trials and Meta-analysis. Total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: inverse variance.

	S	pinal		G	eneral			Mean Difference		Ν	lean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV	, Random, 95%	CI	
Kosam Durga 2014	30	1.3	20	28.3	1.76	20	100.0%	1.70 [0.74, 2.66]					
Total (95% CI)			20			20	100.0%	1.70 [0.74, 2.66]					
Heterogeneity: Not ap Test for overall effect:	plicable Z = 3.47	(P =	0.0005	5)					-100	-50 Favours Spipal Anes	0 thesia Favours	50 Seneral anesthe	100 Psi

Figure 12. Forest plot for mean NACS at 15 minute comparing SA VS GA: individual trials and Meta analysis. Total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: inverse variance.



Figure 13. Forest plot for mean NACS at 2hrs comparing SA VS GA: individual trials and Meta analysis. Total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: inverse variance.



Figure 14. Forest plot for mean NACS at 24 hrs comparing SA VS GA: individual trials and Meta-analysis. Total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: inverse variance.

		S	pinal	General					Mean Difference	Mean Difference					
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl		IV, Random, 95% Cl				
	ABBOUD TK, 1985	83.9	13.5	20	74.4	28.6	20	100.0%	9.50 [-4.36, 23.36]			-			
	Total (95% CI)			20			20	100.0%	9.50 [-4.36, 23.36]	I		•		I	I
Heterogeneity: Not applicable Test for overall effect: Z = 1.34 (P = 0.18)								-100	-5 Favours Sp	0 binal Anesthesia	0 Favours Gene	50 eral Anesthesi	100		

Respiratory support: Respiratory support requirement to neonate was reported in one study [14] and there was no significant difference between General anesthesia 4 (4.4%) and Spinal anesthesia groups 4 (4.2%).

Hypoglycemia and phototherapy: Incidence of hypoglycemia and requirement of phototherapy were reported in one study [14] and there was no significant difference between neonates delivered with general or spinal Anesthesia.

resuscitation at birth was reported in one study [5] and three babies out of twenty required resuscitation at birth who delivered with General Anesthesia as compared to Spinal and Epidural anesthesia who didn't require resuscitation at all.

Quantitative data synthesis

Regional Anesthesia and General anesthesia were compared as intervention and control respectively using Apgar score and umbilical blood gas analysis as the primary outcomes. Nine

Requirement of resuscitation: Requirement of neonatal

studies were included for meta-analysis.

In the pooled Analysis, The Apgar score at one minute less than seven was better in spinal anesthesia when compared to General Anesthesia (OR=0.24, 95% confidence interval (CI) 0.14 to 0.42, 5 trials, 548 participants) [3, 5, 8, 9, 14] (Figure 1). However, there was no significant association at 5th minute Apgar score less than seven (OR=-0.02, 95% CI -0.09 to 0.05, 3 trials, 260 participants) [3, 5, 8] (Figure 2).

There was no significant association between spinal and general anesthesia on neonatal Apgar score at 1^{st} and 5^{th} minute greater than seven (OR= 1.04, 95% CI 0.24 to 4.48, 3 trials, 260 participants) and (OR= 7.19, 95% CI 0.83 to 62.22, 3 trial, 260 participants) respectively [3, 5, 8] (Figure 3&4).

There was no significant mean difference on neonatal mean Apgar score at 1st and 5th minutes between spinal and General anesthesia (MD= -0.08, 95% CI -1.03 to 0.88, 5 trials, 671 participants) [3, 5, 7, 11, 14] (Figure 5). However, there was significant mean difference between spinal and general anesthesia on neonatal mean Apgar score at 5th minute (MD=0.51, 95% CI 0.14 to 0.88, 5 trials, 671 participants) [3, 5, 7, 11, 14] (Figure 6).

There was no significant mean difference between Epidural and General Anesthesia on neonatal mean Apgar score at 1^{st} and 5^{th} minutes (MD=-0.03, 95% CI -1.03 to 2.66, 3 trials, 325 participants) [5, 6, 11] (Figure 7) and (MD=-0.33, 95 % CI -1.63 to 0.98, 2 trials, 285 participants) respectively [6, 11] (Figure 8).

Six studies reported on neonatal umbilical arterial oxygen tension and noted that there was no difference in the standard mean difference (SMD) of umbilical arterial oxygen tension when general anesthesia is compared with spinal anesthesia (SMD= 0.13, 95% CI -0.51 to 0.77, 6 trials, 709 participants) [3, 5, 7, 10, 11, 14] (Figure 9). One study reported on umbilical artery and Venous PH and noted that there was a mean difference when general anesthesia is compared with spinal anesthesia (MD= -0.01, 95% CI -0.002 top -0.00, one trial, 40 participants) and (MD= -0.98, 95% CI -1.66 to -0.30, one trial, 40 participants) [10] (Figure 10).

One study reported Early Neonatal Neurobehavioral Score (ENNS) and noted that there was a significant mean difference when general anesthesia is compared with spinal anesthesia (MD= 1.70, 95% CI 0.24 to 2.66, one trial, 40 participants) [5] (Figure 11).

One study reported neonatal neurobehavioral Adaptive capacity score (NACS) in 15 minutes, 2hrs and 24hrs and noted that there were no difference when general anesthesia is compared with general anesthesia (MD= 9.8, 95% CI -2.02 to 21.62, one trial, 40 participants), (MD= 10.70, 95% CI -2.03 to 23.43, one trial, 40 participants) and (MD= 9.5, 95 % CI -4.36 to 23.36, one trial, 40 participants) respectively [10] (Figure 12, 13 &14).

Discussion

No trial reported on neonatal death and this may indicate the relative safety of cesarean section particularly in the countries where the included studies conducted. Larger sample size would also be required to detect such outcome as most of the included studies were underpowered. In this review, spinal anesthesia appears to be associated with better first minute Apgar score (less than seven Apgar score) as compared to general Anesthesia. However, the mean Apgar score at first and fifth minute didn't show any significant difference when general anesthesia is compared with regional (spinal and epidural) anesthesia.

In pooled analysis, the umbilical arterial and venous PH were higher in regional anesthesia when compared to general anesthesia, but in other review [2] the Umbilical arterial PH didn't show any significant different unlike the Umbilical venous PH which is in line with this review.

The early neonatal neurobehavioral score was higher in spinal anesthesia as compared to general anesthesia. However, neonatal neurobehavioral Adaptive Capacity score at 15min, 2hr and 24hr didn't show any significant difference between general and spinal anesthesia.

Incidence of neonatal ICU admission was higher in spinal anesthesia unlike a systemic review conducted by Cochrane collaboration where neonatal ICU admission is higher in general anesthesia as compared to regional (spinal and epidural) anesthesia and this discrepancy might be due to the low power in this review.

Need for resuscitation was significantly associated with general anesthesia when compared with regional anesthesia. However, a systemic review conducted by Cochrane collaboration didn't show any significant difference when general anesthesia is compared to regional (spinal and epidural) anesthesia [2]. Although regional anesthesia is associated with better neonatal outcomes, there is insignificant difference on neonatal outcomes when general anesthesia is compared with regional anesthesia in elective and semi-urgent cesarean section.

Conclusion

This review shows that Regional Anesthesia (epidural and spinal) is superior over general Anesthesia in certain neonatal outcomes as depicted by the pooled analysis of individual trials. However, there should be further review with individual trials having high power and similar dosage and techniques as most of the individual trials in this review are low powered and different types of outcome assessment techniques which brings high risk of bias and heterogeneity and difficult to come up with strong conclusion. Overall, the choice of Anesthesia technique for cesarean section would depend on the resource availability, set up of the institution and the skill of the Anesthesiology professional.

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