

Suprascapular nerve block and axillary nerve block versus interscalene nerve block for arthroscopic shoulder surgery

A meta-analysis of randomized controlled trials

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Abstract

Background: The interscalene brachial plexus block (ISB) is a commonly used nerve block technique for postoperative analgesia in patients undergoing shoulder arthroscopy surgery; however, it is associated with potentially serious complications. The use of suprascapular nerve block (SSNB) and axillary Nerve Block (ANB) has been reported as an alternative nerve block with fewer reported side effects for shoulder arthroscopy. This review aimed to compare the impact of SSNB and ANB with ISB during shoulder arthroscopy surgery.

Methods: A meta-analysis was conducted to identify relevant randomized or quasirandomized controlled trials involving SSNB and ISB during shoulder arthroscopy surgery. We searched Web of Science, PubMed, Embase, Cochrane Controlled Trials Register, Cochrane Library, Highwire, CNKI, and Wanfang database from 2010 through August 2021.

Results: We identified 641 patients assessed in 10 randomized or quasirandomized controlled trials. Compared with the ISB group, the SSNB+ANB group had higher visual analog scale or numerical rating scale in PACU (P=.03), 4 hour (P=.001), 6 hour after the operation (P=.002), and lower incidence of complications such as Numb/Tingling (P=.001), Weakness (P <.00001), Horner syndrome (P=.001) and Subjective dyspnea (P=.002). No significant difference was found for visual analog scale or numerical rating scale 8 hour (P=.71), 12 hour (P=.17), 16 hour (P=.38), 1day after operation (P=.11), patient satisfaction (P=.38) and incidence of complications such as hoarseness (P=.07) and nausea/vomiting (P=.41) between 2 groups.

Conclusion: Our high-level evidence has established SSNB+ ANB as an effective and safe analgesic technique and a clinically attractive alternative to interscalene block during arthroscopic shoulder surgery, especially for severe chronic obstructive pulmonary disease, obstructive sleep apnea, and morbid obesity. Given our meta-analysis's relevant possible biases, we required more adequately powered and better-designed randomized controlled trial studies with long-term follow-up to reach a firmer conclusion.

Abbreviations: ANB = Axillary Nerve Block, CI = confidence interval, ISB = interscalene block, NRS = numerical rating scale, RCTs = randomized controlled trials, RR = relative risk, SSNB = Suprascapular nerve block, VAS = visual analog scale.

Keywords: arthroscopy, axillary, interscalene, nerve block, regional, shoulder, suprascapular

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XC and HY contributed equally to this work.

Ethics approval and consent to participate was not applicable.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

There is a high incidence reaching up to 45%; of severe intraoperative and postoperative pain associated with arthroscopic shoulder surgery, which is often significant enough to interfere with initial recovery and rehabilitation.^[1] Various peripheral nerve blocks have been used to reduce intraoperative anesthetic requirements to improve rapid recovery and reduce postoperative pain.^[2,3] Of all blocks, Interscalene brachial plexus block (ISB) is the most frequently used block, as it provides adequate postoperative analgesia for 6 to 12 hours.^[4] However, ISB has the potential for some complications. The most common of these complications is phrenic nerve palsy ISB which can result in

diaphragmatic paralysis.^[5,6] Less common complications included respiratory distress, weakness of the arm, hoarseness of voice, Horner's syndrome and brachial plexus neuropathy.^[7–9] Therefore, ISB is contraindicated in patients with contralateral phrenic nerve palsy, severe preexisting respiratory insufficiency due to chronic obstructive pulmonary disease, restrictive pulmonary disease, bronchial asthma, and high body mass index.^[6,10]

Recently, the Combined suprascapular nerve block and axillary nerve block (SSNB+ANB) was proposed to provide anesthesia and postoperative analgesia for shoulder surgery as a safe alternative to ISB.^[1] ISB provides anesthesia for the shoulder joint by blocking C5 and C6 nerve roots, and most of the nerve supply from C5 and C6

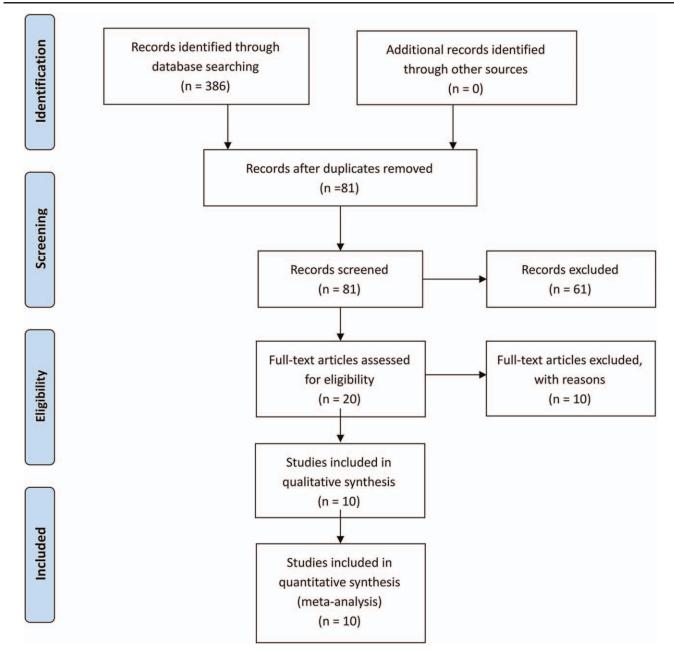


Figure 1. The search results and selection procedure. The literature search identified 386 citations. Of these, we removed 305 duplicates. After reviewing the 81 remaining articles' titles and abstracts, we excluded 61 papers according to the inclusion and exclusion criteria; 20 full texts were retrieved. Because some articles didn't compare the SSBN+ANB with Block ISB, we excluded ten studies. Finally, we identified 641 patients assessed in 10 articles.

Table 1

Characteristics of included studies and patients.

		Sample sizes, n	Age, yr, Mean	%Female	BMI,kg/m ²		
Study	Country		(SSNB/IS	Follow-up	Surgery		
Dhir 2016	Canada	29/30	46.5/51.3	24.1/13.3	29/28.9	7 d	Shoulder arthroscopy
Lee 2012	South Korea	18/26	54/57	44.4/57.7	23.62/24.92	24 h	Arthroscopic rotator cuff
Li 2020	China	40/40	51.1/53	57.5/52.5	22.81/23.39	24 h	Arthroscopic rotator cuff
Luo 2019	China	20/20	48.6/49.6	45/55	24.84/23.91	72 h	Shoulder arthroscopy
Neuts 2018	Belgium	48/50	51/54	62.5/44	26/26	24 h	Shoulder arthroscopy
Pani 2019	India	35/37	37.1/37.7	17.1/21.6	26.027/25.083	24 h	Shoulder arthroscopy
Pitombo 2013	Brazil	34/34	52.2/55	52.9/61.8	26.79/27.95	24 h	Shoulder arthroscopy
Saini 2021	India	35/35	26.97/27.29	11.5/14.3	24.99/24.03	24 h	Arthroscopic Bankart repair
Waleed 2016	Egypt	30/30	28.6/27.4	33.3/36.7	24.32/24.65	24 h	Shoulder arthroscopy
Zanfaly 2015	Egypt	25/25	43.5/44.6	36/44	NA	24 h	Shoulder arthroscopy

AXB = axillary nerves block, BMI = body mass index. ISB = interscalene block, SSNB = suprascapular nerve block.

The detailed baseline characteristics information including country, number of participants, age, gender, BMI, follow-up time and type of surgery.

Table 2

Details of the nerve blocks and anesthesia used.

Study	Localization method	Analgesia used in SSNB + AXB	Analgesia used in ISB	Analgesia used in PACU	Analgesia used in ward	
Dhir 2016	Ultrasound and nerve stimulator guided	15 mL of 0.5% ropivacaine + 15 mL of 0.5% ropivacaine	20 mL of 0.5% ropivacaine.	Ketorolac, acetaminophen	NA	
Lee 2012	Ultrasound and nerve stimulator guided	2% mepivacaine 10 ml and 0.75% ropivacaine 20 ml	2% mepivacaine 5 ml and 0.75% ropivacaine 10 ml	NA	NA	
Li 2020	Ultrasound guided	10 mL of 0.5% ropivacaine + 10 mL of 0.5% ropivacaine	20 mL of 0.5% ropivacaine.	flurbiprofen axetil IV (50mg) was used as rescue analgesia when VAS > 4	flurbiprofen axetil IV (50mg) was used as rescue analgesia when VAS > 4	
Luo 2019	Ultrasound guided	15 mL of 0.25% ropivacaine + 5 mL of 0.25% ropivacaine	20 mL of 0.25% ropivacaine.	NA	NA	
Neuts 2018	Ultrasound guided	10 mL of 0.75% ropivacaine + 10 mL of 0.75% ropivacaine	20 mL of 0.75% ropivacaine	intravenous paracetamol (15 mg/kg 4 times a day), ketorolac (0.5 mg/kg 3 times a day), and PCIA with piritramide (bolus dose = 2 mg and lockout inter- val = 12 min).	NA	
Pani 2019	Ultrasound and nerve stimulator guided	10 mL of 0.75% ropivacaine + 10 mL of 0.75% ropivacaine	10 mL of 0.75% ropivacaine	Paracetamol IV (1 gm) was used as rescue analgesia when VAS > 4	Paracetamol IV (1 gm) was used as rescue analgesia when VAS > 4	
Pitombo 2013	Ultrasound and nerve stimulator guided	15 mL of 0.33% levobupivacaine with epinephrine 1:200,000 + 15 mL of 0.33% levobupivacaine with epinephrine 1:200,000	30 mL of 0.33% levobupivacaine with epinephrine 1:200,000	In case of moderate (> 3 ≤ 6) or severe (> 7) pain, single-dose intravenous morphine (0.04 mg/kg)	NA	
Saini 2021	Ultrasound and nerve stimulator guided	10 mL of 0.5% ropivacaine +10 mL of 0.5% ropivacaine	10 mL of 0.5% ropivacaine	paracetamol 1 g IV was administered on demand or if VAS was ≥ 4	paracetamol 1 g IV was administered on demand or if VAS was \geq 4	
Waleed 2016	Ultrasound guided	10 ml of 0.25% levobupivacaine/10 ml of 0.25% levobupivacaine	20 ml of 0.25% levobupivacaine	NA	NA	
Zanfaly 2015	Ultrasound and nerve stimulator guided	7–10 ml of 0.5% bupivacaine + 7–10 ml of 0.5% bupivacaine	25–30 ml 0.5% bupivacaine	diclofenac natrium (voltaren) IM, every 8 h, If VAS >3 morphine 0.1 mg/kg IM	NA	

ACU = postanesthesia care unit, AXB = axillary nerves block, IM = intramuscular, ISB = interscalene block, IV = intravenous, NRS = numerical rating scale, SSNB = suprascapular nerve block, US = ultrasound, VAS = visual analog scale.

Details of the nerve blocks and anesthesia used to include localization method, analgesia, used in nerve block, analgesia used in PACU and analgesia used in ward.

nerve roots are also carried by suprascapular and the axillary nerves. These two peripheral nerves are responsible for the majority of the sensory innervation of the shoulder.

But there is still a conflicting view in the literature regarding the effect of combined blockade of SSNB and ANB compared with ISB. The purpose of our meta-analysis was to compare the analgesic efficacy of the SSNB+ANB and ISB, which was measured in terms of the visual analog scale (VAS) score or numerical rating scale (NRS) in the first 24 h after surgery and incidence of complications. The secondary aims were to study patient satisfaction scores.

2. Methods

The current meta-analysis was registered on PROSPERO (International prospective register of systematic reviews) and the registration number was CRD42020210385. This meta-analysis was performed using a predetermined protocol following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement to assess the results' quality to make sure our meta-analysis's results reliable and veritable.

2.1. Search strategy

Web of Science, PubMed, Embase, Cochrane Controlled Trials Register, Cochrane Library, Highwire, CNKI, and Wanfang database were searched from 2010 through August 2021. The keywords used were "nerve block," "regional," "suprascapular," "interscalene," "axillary," "shoulder," "arthroscopic in conjunction with Boolean operators "AND" or "OR." We used Review Manager Software for MAC to perform the meta-analysis.

2.2. Inclusion criteria

Studies were eligible if 1. The intervention was patients undergoing shoulder arthroscopic surgery with SSNB+ANB; 2. The comparator was patients undergoing shoulder arthroscopic surgery with ISB 3. The design of the study was a randomized controlled trials (RCTs) or quasirandomized controlled trials.; 4. The studies were required to contain at least one clinical outcome data; The exclusion criteria were as follows: studies with insufficient clinical outcome data.

2.3. Data extraction process

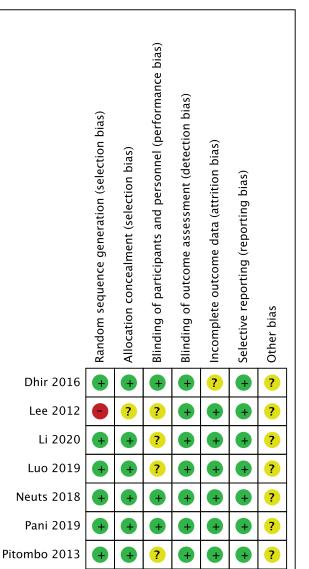
Two reviewers (C.J.S and H.D.Y) used a standardized form to extract data. A third reviewer (X.L.J.) was used to resolve disagreements in eligibility, data extraction, or quality assessment. Extracted data included the primary data based on the following: first author, year of publication, participants, age, gender, body mass index, follow up, type of surgery, Localization method, analgesia Used in nerve block, Analgesia Used in PACU, Analgesia Used in the ward.

2.4. Assessment of studies

We assessed the studies' methodological quality following the Cochrane Handbook's instructions for Systematic Reviews of Interventions.

2.5. Ethical consideration

The adverse effects of the intervention were identified for inclusion in the study and reported as a composite outcome. All included studies had appropriate ethical approval.



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Figure 2. Risk of bias summary for included studies. ?=bias unknown. +=no bias, -=bias. Nine studies adequately described the correct randomization. Nine studies demonstrated sufficient allocation concealment. Six studies described the blinding of participants and personnel. All ten articles described the blinding of outcome assessment and avoided selective reporting. Nine articles retained complete outcome data. We rated as unclear risk of other bias because we can't ignore other potential dangers of biases. As a result, the risk of bias is low or moderate in most of the articles reviewed.

2.6. Statistical analysis

Saini 2021

Waleed 2016

Zanfaly 2015

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+

+

+

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RevMan software (version 5.3; The Cochrane Collaboration) was used for the analysis. We used a random-effects model for all analyses, as clinical heterogeneity was assumed to exist because of differences in standardization in anesthetic, nerve block techniques, diversity of shoulder surgeries performed, and the timing of assessment across studies.

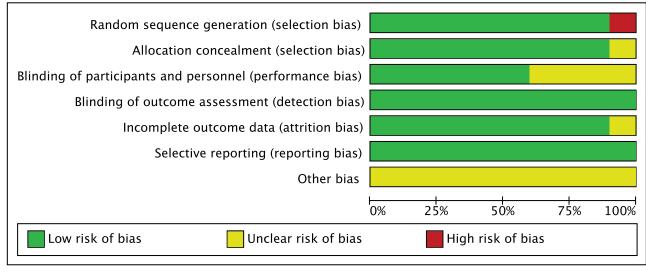


Figure 3. The risk of bias graph. The overall quality of the included studies was considered adequate

Data were summarized as the ratio of relative risk (patient satisfaction, complications including the rate of Numb/Tingling, weakness, horner syndrome, subjective dyspnea, hoarseness, Nausea/vomiting. or the difference between means (VAS or NRS and patient satisfaction). Studies that did not have standard deviations were calculated from p values, confidence intervals, or standard errors. The results were considered as a statistically significant difference when *P* values were less than .05.

3. Results

The literature search identified 386 citations. Of these, we removed 305 duplicates. After reviewing the 81 remaining articles' titles and abstracts, we excluded 61 papers according to the inclusion and exclusion criteria; 20 full texts were retrieved. Because some articles didn't compare the SSBN+ANB with Block ISB, we excluded eight studies. Finally, we identified 641 patients assessed in 10 articles^[10–19] (Fig. 1). Study baseline characteristics and general intervention information are summarized in Tables 1 and 2.

The risk of bias summary and bias graph for RCTs is shown in Figures 2 and 3. Nine studies adequately described the correct randomization. Nine studies demonstrated sufficient allocation concealment. Six studies described the blinding of participants and personnel. All ten articles described the blinding of outcome assessment and avoided selective reporting. Nine articles retained complete outcome data. We rated as unclear risk of other bias because we can't ignore other potential dangers of biases. As a result, the risk of bias is low or moderate in most of the articles reviewed. (Fig. 2).

3.1. VAS or NRS

The pooled results showed that ISB group had lower VAS or NRS in PACU (MD = 1.38, 95% confidence intervals [CI] [0.16,2.60], P=.03 Fig. 4),4 hour after operation (MD=1.78, 95% CI [0.72,2.85], P=.001 Fig. 4). and 6 hour after operation (MD=1.08, 95% CI [0.40, 1.76], P=.002 Fig. 4). No significant

difference was found for VAS or NRS 8 hour after operation (MD=0.3, 95% CI [-1.28,1.88], P=.71 Fig. 4), 12 hours (MD=-0.51, 95% CI [-1.23,0.21], P=.17 Fig. 4), 16 hour (MD=-0.75, 95% CI [-2.4,0.91], P=.38 Fig. 4) and 1day after operation (MD=-0.5, 95% CI [-1.13,0.12], P=.11 Fig. 4) between 2 groups.

3.2. Block related complications

The pooled data showed that SSNB+ ANB group had lower incidence of Numb/Tingling (relative risk [RR]=0.29, 95% CI [0.13,0.61], P=.001 Fig. 5),Weakness (RR=0.11, 95% CI [0.05,0.24], P <.0001 Fig. 5), Horner syndrome (RR=0.09, 95% CI [0.02,0.37], P=.001 Fig. 5) and Subjective dyspnea (RR=0.19, 95% CI [0.07,0.55], P=.002 Fig. 5) No significant difference was found for Hoarseness (RR=0.26, 95% CI [0.06,1.12], P=.07 Fig. 5), and nausea/vomiting (RR=0.8, 95% CI [0.47,1.36], P=.41 Fig. 5).

3.3. Patient satisfaction

We didn't find any significant difference for patient satisfaction (MD=0.31, 95% CI [-0.38,0.99], P=.38 Fig. 6).

4. Discussion

Our study is the first meta-analysis to identify relevant randomized controlled trials or quasirandomized controlled trials involving SSNB+ANB and ISB during arthroscopic shoulder surgery. The postoperative pain at the individual time points suggested that SSNB+ANB may provide inferior pain control limited to the PACU stay, 4 hours and 6 hours after the operation. However, SSNB+ANB was not different from ISB for providing postoperative pain control at other time points for the first 24 hours after surgery. Furthermore, SSBNB+ANB was associated with a lower incidence of numb/tingling, weakness, horner syndrome, and subjective dyspnea. The remaining analgesic outcome results, such as patient satisfaction and other nerve block complications, including Hoarseness and nausea/ vomiting, were consistently not different between the 2 groups.

Study or Subgroup	SSN	B+ANB							
Study or Subgroup		DIAND	,		ISB			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 PACU									
Dhir 2016	5.45	0.52	29	18	0.285	30	3.0%	3.65 [3.44, 3.86]	
Lee 2012	3.6	1.9	18	1.4	1.2	26	2.5%	2.20 [1.21, 3.19]	
Li 2020	1.93	0.62	40	1.73	0.78	40	2.9%	0.20 [-0.11, 0.51]	•
Neuts 2018	2.1	1.11	48	0.1	0.04	50	2.9%	2.00 [1.69, 2.31]	-
Pani 2019	1.76	0.32	35	1.49	0.35	37	3.0%	0.27 [0.12, 0.42]	-
Saini 2021	0.7	1.55	35	0	0	35		Not estimable	
Waleed 2016	0.57	0.27	30	0.53	0.18	30	3.0%	0.04 [-0.08, 0.16]	+
Subtotal (95% CI)	0.57	0.2.	235	0.55	0.10	248	17.3%	1.38 [0.16, 2.60]	
Heterogeneity: Tau ² = Test for overall effect				df = 5	(P < 0.0				-
	ι. z = z.z	2 (P = ().05)						
1.1.4 4h									
Luo 2019	6.2	2.4	20	2.9	1.1	20	2.4%	3.30 [2.14, 4.46]	
Neuts 2018	2.9	1.08	48	0.1	0.05	50	2.9%	2.80 [2.49, 3.11]	-
Pani 2019	3.16	0.32	35	2.44	0.33	37	3.0%	0.72 [0.57, 0.87]	*
Saini 2021	3.42	3.1	35	1	1.55	35	2.4%	2.42 [1.27, 3.57]	
									L
Waleed 2016	1.76	0.5	30	1.64	0.45	30	3.0%	0.12 [-0.12, 0.36]	
Subtotal (95% CI)		_	168			172	13.7%	1.78 [0.72, 2.85]	
Heterogeneity: Tau ² = Test for overall effect					(P < 0.0	0001);	$l^2 = 98\%$		
1.1.5 6h									
Dhir 2016	л	1.005	26	2.35	0.58	20	2 0%	1 65 [1 22 2 08]	
			28			28	2.9%	1.65 [1.22, 2.08]	L
Li 2020	2.2	0.61	40	2.08	0.53	40	3.0%	0.12 [-0.13, 0.37]	Г
Luo 2019	6.5	1.1	20	2.5	1.7	20	2.6%	4.00 [3.11, 4.89]	
Pani 2019	5.19	0.31	35	4.83	0.34	37	3.0%	0.36 [0.21, 0.51]	*
Saini 2021	2.71	4.64	35	1.29	1.55	35	2.0%	1.42 [-0.20, 3.04]	+
Waleed 2016	2.97	0.66	30	3.18	0.57	30	2.9%	-0.21 [-0.52, 0.10]	-+
Subtotal (95% CI)	2.57	0.00	188	5.10	5.57	190	16.4%	1.08 [0.40, 1.76]	
Heterogeneity: Tau ² =	= 0.62; C	$hi^2 = 1$		df = 5	(P < 0.0			1.00 [0.40, 1.70]	
Test for overall effect	t: Z = 3.1	0 (P = 0).002)						
1.1.6 8 h									
1.1.0 0 11					2.0	26	2.1%	-1.30 [-2.81, 0.21]	
	2.0	2.2	10						
Lee 2012	3.9	2.2	18	5.2	2.9	26			
Lee 2012 Neuts 2018	1.9	0.53	48	0.1	0.06	50	3.0%	1.80 [1.65, 1.95]	· · ·
Lee 2012			48 25			50 25			
Lee 2012 Neuts 2018	1.9	0.53	48	0.1	0.06	50	3.0%	1.80 [1.65, 1.95]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² =	1.9 4 = 1.78; C	0.53 0.25 hi ² = 8	48 25 91 0.79, d	0.1 4	0.06 1	50 25 101	3.0% 2.9% 8.0%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect	1.9 4 = 1.78; C	0.53 0.25 hi ² = 8	48 25 91 0.79, d	0.1 4	0.06 1	50 25 101	3.0% 2.9% 8.0%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h	1.9 4 = 1.78; C t: Z = 0.3	0.53 0.25 hi ² = 8 7 (P = 0	48 25 91 0.79, d 0.71)	0.1 4 f = 2 (F	0.06 1 ? < 0.00	50 25 101	3.0% 2.9% 8.0% ² = 98%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect	1.9 4 = 1.78; C	0.53 0.25 hi ² = 8	48 25 91 0.79, d	0.1 4	0.06 1	50 25 101	3.0% 2.9% 8.0%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020	1.9 4 = 1.78; C t: Z = 0.3 2.45	0.53 0.25 $hi^2 = 80$ 7 (P = 0) 0.55	48 25 91 0.79, d).71) 40	0.1 4 If = 2 (F 2.23	0.06 1 9 < 0.00 0.58	50 25 101 0001); 1 40	3.0% 2.9% 8.0% $^{2} = 98\%$ 3.0%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018	1.9 4 = 1.78; C t: Z = 0.3 2.45 3	0.53 0.25 $hi^2 = 80$ 7 (P = 0) 0.55 0.79	48 25 91 0.79, d 0.71) 40 48	0.1 4 f = 2 (F 2.23 3	0.06 1 9 < 0.00 0.58 1.1	50 25 101 9001); 1 40 50	3.0% 2.9% 8.0% 2 = 98% 3.0% 2.9%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019	1.9 4 = 1.78; C t: Z = 0.3 2.45 3 3.98	$0.53 \\ 0.25 \\ hi^2 = 80 \\ 7 (P = 0) \\ 0.55 \\ 0.79 \\ 0.32 \\ 0.53$	48 25 91 0.79, d 0.71) 40 48 35	0.1 4 f = 2 (F 2.23 3 5.12	0.06 1 ? < 0.00 0.58 1.1 0.35	50 25 101 0001); I 40 50 37	3.0% 2.9% 8.0% ² = 98% 3.0% 3.0%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021	1.9 4 = 1.78; C t: Z = 0.3 2.45 3 3.98 1	0.53 0.25 hi ² = 80 7 (P = 0 0.55 0.79 0.32 1.55	48 25 91 0.79, d 0.71) 40 48 35 35	0.1 4 if = 2 (F 2.23 3 5.12 3.93	0.06 1 ? < 0.00 0.58 1.1 0.35 5.41	50 25 101 0001); 1 40 50 37 35	$3.0\% \\ 2.9\% \\ 8.0\% \\ 2 = 98\% \\ 3.0\% \\ 2.9\% \\ 3.0\% \\ 1.8\% \\ 3.0\% \\ 1.8\% \\ 3.0\%$	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016	1.9 4 = 1.78; C t: Z = 0.3 2.45 3 3.98	$0.53 \\ 0.25 \\ hi^2 = 80 \\ 7 (P = 0) \\ 0.55 \\ 0.79 \\ 0.32 \\ 0.53$	48 25 91 0.79, d 0.71) 40 48 35 35 30	0.1 4 f = 2 (F 2.23 3 5.12	0.06 1 ? < 0.00 0.58 1.1 0.35	50 25 101 0001); 1 40 50 37 35 30	3.0% 2.9% 8.0% $^{2} = 98\%$ 3.0% 2.9% 3.0% 1.8% 3.0%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021	1.9 4 = 1.78; C t: Z = 0.3 2.45 3 3.98 1	0.53 0.25 hi ² = 80 7 (P = 0 0.55 0.79 0.32 1.55	48 25 91 0.79, d 0.71) 40 48 35 35	0.1 4 if = 2 (F 2.23 3 5.12 3.93	0.06 1 ? < 0.00 0.58 1.1 0.35 5.41	50 25 101 0001); 1 40 50 37 35	3.0% 2.9% 8.0% $^{2} = 98\%$ 3.0% 2.9% 3.0% 1.8% 3.0%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² =	1.9 4 = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C	$0.53 \\ 0.25 \\ hi^2 = 8i \\ 7 (P = 0) \\ 0.55 \\ 0.79 \\ 0.32 \\ 1.55 \\ 0.5 \\ hi^2 = 1$	48 25 91 0.79, d 0.71) 40 48 35 35 30 188 16.98,	0.1 4 f = 2 (F 2.23 3 5.12 3.93 3.39	0.06 1 9 < 0.00 0.58 1.1 0.35 5.41 0.55	50 25 101 9001); I 40 50 37 35 30 192	3.0% 2.9% 8.0% 2 = 98% 3.0% 2.9% 3.0% 1.8% 3.0% 13.6%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect	1.9 4 = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C	$0.53 \\ 0.25 \\ hi^2 = 8i \\ 7 (P = 0) \\ 0.55 \\ 0.79 \\ 0.32 \\ 1.55 \\ 0.5 \\ hi^2 = 1$	48 25 91 0.79, d 0.71) 40 48 35 35 30 188 16.98,	0.1 4 f = 2 (F 2.23 3 5.12 3.93 3.39	0.06 1 9 < 0.00 0.58 1.1 0.35 5.41 0.55	50 25 101 9001); I 40 50 37 35 30 192	3.0% 2.9% 8.0% 2 = 98% 3.0% 2.9% 3.0% 1.8% 3.0% 13.6%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h	1.9 4 = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3	0.53 0.25 $hi^2 = 86$ 7 (P = 0 0.55 0.79 0.32 1.55 0.5 $hi^2 = 1$ 9 (P = 0	48 25 91 0.79, d 0.71) 40 48 35 30 188 16.98, 0.17)	0.1 4 f = 2 (F 2.23 3 5.12 3.93 3.39 df = 4	0.06 1 0.58 1.1 0.35 5.41 0.55 (P < 0.0	50 25 101 0001); F 40 50 37 35 30 192 00001);	3.0% 2.9% 8.0% 2 = 98% 3.0% 3.0% 1.8% 3.0% 13.6% ² = 97%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect	1.9 4 = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C	$0.53 \\ 0.25 \\ hi^2 = 8i \\ 7 (P = 0) \\ 0.55 \\ 0.79 \\ 0.32 \\ 1.55 \\ 0.5 \\ hi^2 = 1$	48 25 91 0.79, d 0.71) 40 48 35 35 30 188 16.98,	0.1 4 f = 2 (F 2.23 3 5.12 3.93 3.39	0.06 1 9 < 0.00 0.58 1.1 0.35 5.41 0.55	50 25 101 9001); I 40 50 37 35 30 192	3.0% 2.9% 8.0% 2 = 98% 3.0% 3.0% 1.8% 3.0% 13.6% ² = 97%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h	1.9 4 = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3	0.53 0.25 $hi^2 = 86$ 7 (P = 0 0.55 0.79 0.32 1.55 0.5 $hi^2 = 1$ 9 (P = 0	48 25 91 0.79, d 0.71) 40 48 35 30 188 16.98, 0.17)	0.1 4 f = 2 (F 2.23 3 5.12 3.93 3.39 df = 4 4.8	0.06 1 0.58 1.1 0.35 5.41 0.55 (P < 0.0	50 25 101 0001); F 40 50 37 35 30 192 00001);	3.0% 2.9% 8.0% 2 = 98% 3.0% 3.0% 1.8% 3.0% 13.6% ² = 97%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015	1.9 4 = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1	0.53 0.25 $hi^2 = 8i$ 7 (P = 0 0.55 0.79 0.32 1.55 0.5 $hi^2 = 1$ 9 (P = 0 2.1	48 25 91 0.79, d 0.71) 40 48 35 30 188 16.98, 0.17) 18	0.1 4 f = 2 (F 2.23 3 5.12 3.93 3.39 df = 4 4.8	0.06 1 	50 25 101 9001); F 40 50 37 35 30 192 90001); 26	3.0% 2.9% 8.0% $^2 = 98\%$ 3.0% 2.9% 3.0% 1.8% 3.0% 13.6% $1^2 = 97\%$ 2.4% 3.0%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI)	$1.9 \\ 4$ = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4	0.53 0.25 $hi^2 = 8i$ 7 (P = 0 0.55 0.79 0.32 1.55 0.5 $hi^2 = 1i$ 9 (P = 0 2.1 0.25	48 25 91 0.79, d 0.71) 40 48 35 30 188 16.98, 0.17) 18 25 43	$0.1 \\ 4 \\ f = 2 (F \\ 2.23 \\ 3 \\ 5.12 \\ 3.93 \\ 3.39 \\ df = 4 \\ 4.8 \\ 4$	0.06 1	50 25 101 0001); f 40 50 37 35 30 192 00001); 26 25 51	$\begin{array}{c} 3.0\%\\ 2.9\%\\ \textbf{8.0\%}\\ ^2=98\%\\ \end{array}$ $\begin{array}{c} 3.0\%\\ 2.9\%\\ 3.0\%\\ \textbf{1.8\%}\\ \textbf{3.0\%}\\ \textbf{13.6\%}\\ \textbf{13.6\%}\\ \textbf{1}^2=97\%\\ \end{array}$ $\begin{array}{c} 2.4\%\\ \textbf{3.0\%}\\ \textbf{5.4\%}\\ \end{array}$	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015	$1.9 \\ 4$ = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C	$\begin{array}{c} 0.53\\ 0.25\\ \text{hi}^2 = 80\\ 7 \ (\text{P} = 0\\ 0.55\\ 0.79\\ 0.32\\ 1.55\\ 0.5\\ \text{hi}^2 = 1\\ 9 \ (\text{P} = 0\\ 2.1\\ 0.25\\ \text{hi}^2 = 7. \end{array}$	48 25 91 0.79, d 0.71) 40 48 35 30 188 16.98, 0.17) 18 25 43 .93, df	$0.1 \\ 4 \\ f = 2 (F \\ 2.23 \\ 3 \\ 5.12 \\ 3.93 \\ 3.39 \\ df = 4 \\ 4.8 \\ 4$	0.06 1	50 25 101 0001); f 40 50 37 35 30 192 00001); 26 25 51	$\begin{array}{c} 3.0\%\\ 2.9\%\\ \textbf{8.0\%}\\ ^2=98\%\\ \end{array}$ $\begin{array}{c} 3.0\%\\ 2.9\%\\ 3.0\%\\ \textbf{1.8\%}\\ \textbf{3.0\%}\\ \textbf{13.6\%}\\ \textbf{13.6\%}\\ \textbf{1}^2=97\%\\ \end{array}$ $\begin{array}{c} 2.4\%\\ \textbf{3.0\%}\\ \textbf{5.4\%}\\ \end{array}$	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saint 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect	$1.9 \\ 4$ = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C	$\begin{array}{c} 0.53\\ 0.25\\ \text{hi}^2 = 80\\ 7 \ (\text{P} = 0\\ 0.55\\ 0.79\\ 0.32\\ 1.55\\ 0.5\\ \text{hi}^2 = 1\\ 9 \ (\text{P} = 0\\ 2.1\\ 0.25\\ \text{hi}^2 = 7. \end{array}$	48 25 91 0.79, d 0.71) 40 48 35 30 188 16.98, 0.17) 18 25 43 .93, df	$0.1 \\ 4 \\ f = 2 (F \\ 2.23 \\ 3 \\ 5.12 \\ 3.93 \\ 3.39 \\ df = 4 \\ 4.8 \\ 4$	0.06 1	50 25 101 0001); f 40 50 37 35 30 192 00001); 26 25 51	$\begin{array}{c} 3.0\%\\ 2.9\%\\ \textbf{8.0\%}\\ ^2=98\%\\ \end{array}$ $\begin{array}{c} 3.0\%\\ 2.9\%\\ 3.0\%\\ \textbf{1.8\%}\\ \textbf{3.0\%}\\ \textbf{13.6\%}\\ \textbf{13.6\%}\\ \textbf{1}^2=97\%\\ \end{array}$ $\begin{array}{c} 2.4\%\\ \textbf{3.0\%}\\ \textbf{5.4\%}\\ \end{array}$	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d	$1.9 \\ 4$ = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8	$\begin{array}{l} 0.53\\ 0.25\\ hi^2 = 8i\\ 7\ (P = (\\ 0.55\\ 0.79\\ 0.32\\ 1.55\\ 0.5\\ hi^2 = 1\\ 9\ (P = (\\ 0.25\\ hi^2 = 7.\\ 9\ (P = (\\ 0.25\\ hi^2 = 7.\\ 0\ (P = (\\ 0\ $	48 25 97, d 0.71) 40 48 35 35 35 35 36 188 16.98, 0.17) 18 25 43 99, df 0.38)	0.1 4 f = 2 (F 2.23 3 5.12 3.93 3.39 df = 4 4.8 4 4 = 1 (P	$\begin{array}{c} 0.06 \\ 1 \\ 0.58 \\ 1.1 \\ 0.35 \\ 5.41 \\ 0.55 \\ (P < 0.0 \\ 1.7 \\ 0.375 \\ = 0.005 \end{array}$	50 25 101 40 50 37 35 37 35 30 92 90001); 1 ² = 1	3.0% 2.9% 8.0% $^2 = 98\%$ 3.0% 2.9% 3.0% 1.8% 3.0% 1.8% 3.0% 1.8% 3.0% 1.8% 3.0% 1.8% 3.0% 5.4% 3.7%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016	1.9 4 = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8 \\ 7 \ (P = (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,$	48 25 91 0.779, d 0,71) 40 48 35 35 30 188 25 43 93, df 0.38) 27	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	0.06 1 0.58 1.1 0.35 5.41 0.55 (P < 0.0) 1.7 0.375 = 0.005 0.6	50 25 101 40 50 37 35 30 192 200001); 1 ² = 1 23	3.0% 2.9% 8.0% $2^{2} = 98\%$ 3.0% 2.9% 3.0% 13.6% $1^{2} = 97\%$ 2.4% 3.0% 5.4% 2.9%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012	$1.9 \\ 4$ = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92 3.1	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8 \\ 7 \ (P = (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,$	48 255 91 0.79, d 40 48 35 30 188 16.98, 0.17) 18 25 43 93, df 0.38) 27 18	0.1 4 f = 2 (f 2.23 3 5.12 3.93 3.39 df = 4 4.8 4 4 = 1 (P 6.35 3.9	$\begin{array}{c} 0.06 \\ 1 \\ 2 < 0.00 \\ 0.58 \\ 1.1 \\ 0.35 \\ 5.41 \\ 0.55 \\ (P < 0.0 \\ 1.7 \\ 0.375 \\ = 0.005 \\ 0.6 \\ 2.1 \end{array}$	50 25 101 0001); F 40 50 37 35 30 192 00001); ; I ² = i 23 23 26	3.0% 2.9% 8.0% $2^{2} = 98\%$ 3.0% 2.9% 3.0% 13.6% $1^{2} = 97\%$ 2.4% 3.0% 5.4% 3.7% 2.9% 2.9% 2.4%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91] -2.43 [-2.79, -2.07] -0.80 [-1.89, 0.29]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012	1.9 4 = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8 \\ 7 \ (P = (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,$	48 25 91 0.779, d 0,71) 40 48 35 35 30 188 25 43 93, df 0.38) 27	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	0.06 1 0.58 1.1 0.35 5.41 0.55 (P < 0.0) 1.7 0.375 = 0.005 0.6	50 25 101 40 50 37 35 30 192 200001); 1 ² = 1 23	3.0% 2.9% 8.0% $2^{2} = 98\%$ 3.0% 2.9% 3.0% 13.6% $1^{2} = 97\%$ 2.4% 3.0% 5.4% 2.9%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012	$1.9 \\ 4$ = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92 3.1	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8 \\ 7 \ (P = (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,$	48 255 91 0.79, d 40 48 35 30 188 16.98, 0.17) 18 25 43 93, df 0.38) 27 18	0.1 4 f = 2 (f 2.23 3 5.12 3.93 3.39 df = 4 4.8 4 4 = 1 (P 6.35 3.9	$\begin{array}{c} 0.06 \\ 1 \\ 2 < 0.00 \\ 0.58 \\ 1.1 \\ 0.35 \\ 5.41 \\ 0.55 \\ (P < 0.0 \\ 1.7 \\ 0.375 \\ = 0.005 \\ 0.6 \\ 2.1 \end{array}$	50 25 101 0001); F 40 50 37 35 30 192 00001); ; I ² = i 23 23 26	3.0% 2.9% 8.0% $2^{2} = 98\%$ 3.0% 2.9% 3.0% 13.6% $1^{2} = 97\%$ 2.4% 3.0% 5.4% 3.7% 2.9% 2.9% 2.4%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91] -2.43 [-2.79, -2.07] -0.80 [-1.89, 0.29]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012 Li 2020 Luo 2019	$1.9 \\ 4$ = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92 3.1 3.18 3.9	$\begin{array}{c} 0.53\\ 0.25\\ \text{hi}^2 = 86\\ 7\ (\text{P} = (0,0,0,0,0)\\ 0.32\\ 1.55\\ 0.5\\ 0.5\\ 1.55\\ 0.5\\ 0.5\\ 1.55\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ $	48 25 30 30,77, d 30,71, d 30,71, d 40 40 48 35 35 35 30 188 16.98, 0.17) 18 25 43 93, df 0.38) 27 18 8 40 20	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	$\begin{array}{c} 0.06 \\ 1 \\ 0.58 \\ 1.1 \\ 0.35 \\ 5.41 \\ 0.55 \\ (P < 0.0 \\ 1.7 \\ 0.375 \\ = 0.005 \\ 0.6 \\ 2.1 \\ 0.57 \\ 1.4 \end{array}$	50 25 101 40 50 37 35 35 30 192 10001); if 2 26 25 51 23 26 25 51 23 26 40 20	3.0% 2.9% 8.0% 2 = 98% 3.0% 2.9% 3.0% 1.8% 3.0% 1.6% $1^2 = 97\%$ 2.4% 3.0% 5.4% 37% 2.9% 2.9% 2.9% 2.9% 2.5%	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91] -2.43 [-2.79, -2.07] -0.80 [-1.89, 0.29] 0.10 [-0.17, 0.37] 0.80 [-0.17, 1.77]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012 Li 2020 Liuo 2019 Neuts 2018	$1.9 \\ 4$ = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92 3.1 3.18 3.99 2.9	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8(7)\\ P = (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,$	48 255 91 0.77, d 40 48 35 30 188 16.98, 0.17) 18 85 43 93, df 0.38) 27 18 40 0.27 18 40 40 48 25 43 93, df 0.38)	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	0.06 1 0.58 1.1 0.55 5.41 0.55 (P < 0.0) 1.7 0.375 = 0.005 0.6 2.1 0.59	50 25 101 40001); F 50 37 35 30 192 200001); 7 26 25 51 1 23 26 40 00 20 50 50	$\begin{array}{c} 3.0\%\\ 2.9\%\\ \textbf{8.0\%}\\ ^2=98\%\\ \end{array}\\ \begin{array}{c} 3.0\%\\ 2.9\%\\ 3.0\%\\ \textbf{13.6\%}\\ \textbf{13.6\%}\\ \textbf{1}^2=97\%\\ \end{array}\\ \begin{array}{c} 2.4\%\\ \textbf{3.0\%}\\ \textbf{5.4\%}\\ \textbf{37\%}\\ \end{array}$	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91] -2.43 [-2.79, -2.07] -0.80 [-1.89, 0.29] 0.10 [-0.17, 1.77] -0.20 [-0.46, 0.06]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012 Li 2020 Luo 2019 Neuts 2018 Pani 2019	$1.9 \\ 4$ = 1.78; C = 0.38; C t: Z = 0.3 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92 3.1 3.18 3.9 2.9 2.06	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8 \\ 7 \ (P = (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,$	48 255 91 	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	$\begin{array}{c} 0.06 \\ 1 \\ 0.58 \\ 1.1 \\ 0.35 \\ 5.41 \\ 0.55 \\ (P < 0.0 \\ 1.7 \\ 0.375 \\ = 0.005 \\ 0.6 \\ 2.1 \\ 0.57 \\ 1.4 \\ 0.59 \\ 0.35 \end{array}$	50 25 101 0001); F 40 50 37 35 30 192 00001); ; I ² = i 23 26 40 20 20 50 37	$\begin{array}{c} 3.0\%\\ 2.9\%\\ \textbf{8.0\%}\\ 2^{2}=98\%\\ \end{array}\\ \begin{array}{c} 3.0\%\\ 2.9\%\\ 3.0\%\\ \textbf{13.6\%}\\ \textbf{13.6\%}\\ \textbf{13.6\%}\\ \textbf{13.6\%}\\ \textbf{2.9\%}\\ \textbf{3.0\%}\\ \textbf{5.4\%}\\ \textbf{3.0\%}\\ \textbf{5.4\%}\\ \textbf{3.0\%}\\ \textbf{3.0\%}\\ \textbf{3.0\%}\\ \textbf{3.0\%}\\ \end{array}$	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91] -2.43 [-2.79, -2.07] -0.80 [-1.89, 0.29] 0.10 [-0.17, 0.37] 0.80 [-0.17, 1.77] -0.20 [-0.46, 0.06] -1.64 [-1.79, -1.49]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012 Li 2020 Luo 2019 Neuts 2018 Pani 2019 Saini 2021	$1.9 \\ 4$ = 1.78; C = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92 3.1 3.18 3.9 2.9 2.06 0.36	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8t\\ 7 \ (P = 0\\ 0.55\\ 0.79\\ 0.32\\ 1.55\\ 0.5\\ hi^2 = 1\\ 9 \ (P = 0\\ 0.25\\ hi^2 = 7\\ .\\ 0.25\\ hi^2 = 7\\ .\\ 0.7\\ 1.6\\ 0.64\\ 1.7\\ 0.73\\ 0.31\\ 0.77\\ \end{array}$	48 25 91 0.79, d 40 48 35 30 188 16.98, 0.17) 18 25 43 93, df 18, 33 16.98, 0.17) 18 8 25 43 93, df 18 35 35 35	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	$\begin{array}{c} 0.06 \\ 1 \\ 0.58 \\ 1.1 \\ 0.35 \\ 5.41 \\ 0.55 \\ (P < 0.0 \\ 1.7 \\ 0.375 \\ = 0.005 \\ 0.6 \\ 2.1 \\ 0.57 \\ 1.4 \\ 0.59 \\ 0.35 \\ 0.77 \end{array}$	$\begin{array}{c} 50\\ 25\\ 101\\ 0001); \ f \\ \\ 40\\ 50\\ 37\\ 35\\ 30\\ 192\\ 00001); \ l^2 = i\\ \\ 25\\ 51\\ 23\\ 26\\ 40\\ 20\\ 50\\ 37\\ 35\\ \end{array}$	3.0% 2.9% 8.0% 2 = 98% 3.0% 2.9% 3.0% 1.8% 3.0% 13.6% $1^2 = 97\%$ 2.4% 3.0% 5.4% 3.0% 2.9% 3.0% 2.5% 3.0% 2.5% 3.0% 2.9% 3.0% 2.9% 3.0% 3.0% 2.9% 3.0	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91] -2.43 [-2.79, -2.07] -0.80 [-1.89, 0.29] 0.10 [-0.17, 0.37] 0.80 [-0.17, 1.77] -0.20 [-0.46, 0.06] -1.64 [-1.79, -1.49] 0.00 [-0.36, 0.36]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saint 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012 Li 2020	$1.9 \\ 4$ = 1.78; C = 0.38; C t: Z = 0.3 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92 3.1 3.18 3.9 2.9 2.06	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8 \\ 7 \ (P = (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,$	48 255 91 	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	$\begin{array}{c} 0.06 \\ 1 \\ 0.58 \\ 1.1 \\ 0.35 \\ 5.41 \\ 0.55 \\ (P < 0.0 \\ 1.7 \\ 0.375 \\ = 0.005 \\ 0.6 \\ 2.1 \\ 0.57 \\ 1.4 \\ 0.59 \\ 0.35 \end{array}$	50 25 101 0001); F 40 50 37 35 30 192 00001); ; I ² = i 23 26 40 20 20 50 37	$\begin{array}{c} 3.0\%\\ 2.9\%\\ \textbf{8.0\%}\\ 2^{2}=98\%\\ \end{array}\\ \begin{array}{c} 3.0\%\\ 2.9\%\\ 3.0\%\\ \textbf{13.6\%}\\ \textbf{13.6\%}\\ \textbf{13.6\%}\\ \textbf{13.6\%}\\ \textbf{2.9\%}\\ \textbf{3.0\%}\\ \textbf{5.4\%}\\ \textbf{3.0\%}\\ \textbf{5.4\%}\\ \textbf{3.0\%}\\ \textbf{3.0\%}\\ \textbf{3.0\%}\\ \textbf{3.0\%}\\ \end{array}$	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91] -2.43 [-2.79, -2.07] -0.80 [-1.89, 0.29] 0.10 [-0.17, 0.37] 0.80 [-0.17, 1.77] -0.20 [-0.46, 0.06] -1.64 [-1.79, -1.49]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012 Li 2020 Luo 2019 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016	$1.9 \\ 4$ = 1.78; C t: Z = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92 3.1 3.18 3.9 2.9 2.06 0.36 3.07	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8 \\ 7 \ (P = 0 \\ 0.55\\ 0.79\\ 0.32\\ 1.55\\ 0.5\\ hi^2 = 1\\ 0.25\\ hi^2 = 7\\ 0.9 \ (P = 0 \\ 0.64\\ 1.7\\ 0.73\\ 0.31\\ 0.31\\ 0.77\\ 0.43\\ \end{array}$	48 25 0.79, d .71) 40 40 48 35 30 188 16.98, 0.17) 18 25 43 93, df 0.38) 27 18 40 20 48 35 30 20 20 48 35 30 20 20 20 20 20 20 20 20 20 20 20 20 20	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	0.06 1 0.58 1.1 0.35 5.41 0.55 (P < 0.0) 1.7 0.375 = 0.005 0.6 2.1 0.57 1.4 0.59 0.77 0.47	50 25 101 40 50 37 35 30 90001); I ² = 1 23 23 23 23 24 20 2001); I ² = 1 23 23 23 23 23 20 20 37 35 30	3.0% 2.9% 8.0% 2 = 98% 3.0% 2.9% 3.0% 1.8% 3.0% 1.6% 1.6% 3.0% 2.4% 3.0% 5.4% 3.0% 2.9% 3.0% 2.9% 3.0% 2.5% 3.0% 2.5% 3.0% 2.9% 3.0% 2.5% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.4% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 3.0% 2.9% 3.0% 3	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91] -2.43 [-2.79, -2.07] -0.80 [-1.89, 0.29] 0.10 [-0.17, 0.37] 0.80 [-0.17, 1.77] -0.20 [-0.46, 0.06] -1.64 [-1.79, -1.49] 0.00 [-0.36, 0.36] -0.18 [-0.41, 0.05]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012 Li 2020 Luo 2019 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Zanfaly 2015	$1.9 \\ 4$ = 1.78; C = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92 3.1 3.18 3.9 2.9 2.06 0.36	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8t\\ 7 \ (P = 0\\ 0.55\\ 0.79\\ 0.32\\ 1.55\\ 0.5\\ hi^2 = 1\\ 9 \ (P = 0\\ 0.25\\ hi^2 = 7\\ .\\ 0.25\\ hi^2 = 7\\ .\\ 0.7\\ 1.6\\ 0.64\\ 1.7\\ 0.73\\ 0.31\\ 0.77\\ \end{array}$	48 255 91 0.77, d 40 48 35 30 188 16.98, 0.17) 188 25 43 93, df 0.38) 27 18 40 20 20 48 35 535 30 25	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	$\begin{array}{c} 0.06 \\ 1 \\ 0.58 \\ 1.1 \\ 0.35 \\ 5.41 \\ 0.55 \\ (P < 0.0 \\ 1.7 \\ 0.375 \\ = 0.005 \\ 0.6 \\ 2.1 \\ 0.57 \\ 1.4 \\ 0.59 \\ 0.35 \\ 0.77 \end{array}$	50 25 101 0001); I' 40 50 37 35 50 192 00001); I' 26 55 51 23 26 40 20 20 50 37 35 30 25 51	3.0% 2.9% 8.0% 2 = 98% 3.0% 2.9% 3.0% 13.6% $1^2 = 97\%$ 2.4% 3.0% 5.4% 3.0% 2.9% 3.0	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.30 [-1.28, 1.88] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91] -2.43 [-2.79, -2.07] -0.80 [-1.89, 0.29] 0.10 [-0.17, 0.37] 0.80 [-0.17, 1.77] -0.20 [-0.46, 0.06] -1.64 [-1.79, -1.49] 0.00 [-0.36, 0.36] -0.18 [-0.41, 0.05] 0.00 [-0.14, 0.14]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012 Li 2020 Luo 2019 Neuts 2018 Pani 2021 Waleed 2016 Zanfaly 2015 Subtotal (95% CI)	$1.9 \\ 4$ = 1.78; C = 0.3 2.45 3.98 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C = 0.8 3.92 3.1 3.18 3.9 2.96 0.36 3.07 6	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8 \\ 7 \ (P = (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,$	48 255 91 	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	0.06 1 0.58 1.1 0.35 5.41 0.55 (P < 0.0 1.7 0.375 = 0.005 0.6 2.1 0.57 1.4 0.59 0.35 0.77 0.47 0.25	50 25 101 0001); F 40 50 37 35 30 192 00001); ; I ² = i 23 26 25 51 1 23 26 40 20 50 37 35 51 286	3.0% 2.9% 8.0% 2 = 98% 3.0% 2.9% 3.0% 13.6% 1 ² = 97% 2.4% 3.0% 5.4% 3.7% 2.9% 2.9% 2.9% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 3.0% 3.0% 3.0% 3.0% 3.0% 3.0% 3.0	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.22 [-0.03, 0.47] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91] -2.43 [-2.79, -2.07] -0.80 [-1.89, 0.29] 0.10 [-0.17, 0.37] 0.80 [-0.17, 1.77] -0.20 [-0.46, 0.06] -1.64 [-1.79, -1.49] 0.00 [-0.36, 0.36] -0.18 [-0.41, 0.05]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012 Li 2020 Luo 2019 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Zanfaly 2015	$1.9 \\ 4$ = 1.78; C z.45; 3 3.98; 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92; 3.1 3.18; 3.9 2.96; 0.36; 3.07; 6 = 0.84; C	$\begin{array}{c} 0.53\\ 0.25\\ hi^2 = 8t\\ 7 \ (P = 0\\ 0.55\\ 0.79\\ 0.32\\ 1.55\\ 0.5\\ hi^2 = 1\\ 9 \ (P = 0\\ 0.25\\ hi^2 = 7\\ .9 \ (P = 0\\ 0.7\\ 1.6\\ 0.64\\ 1.7\\ 0.73\\ 0.31\\ 0.77\\ 0.43\\ 0.25\\ hi^2 = 4\end{array}$	48 255 91 0.79, d 40 48 35 30 188 16.98, 0.17) 18 25 30 188 16.98, 0.17) 18 40 20 48 40 20 48 40 20 48 40 20 535 18 18 93, df 18 93, df 19 93, df 18 93, df 18 93, df 18 93, df 18 93, df 18 93, df 19 93, df 18 93, df 19 93, df 19 93, df 18 93, df 19 93, df 19 94 94 95 95 95 95 95 95 95 95 95 95 95 95 95	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	0.06 1 0.58 1.1 0.35 5.41 0.55 (P < 0.0 1.7 0.375 = 0.005 0.6 2.1 0.57 1.4 0.59 0.35 0.77 0.47 0.25	50 25 101 0001); F 40 50 37 35 30 192 00001); ; I ² = i 23 26 25 51 1 23 26 40 20 50 37 35 51 286	3.0% 2.9% 8.0% 2 = 98% 3.0% 2.9% 3.0% 13.6% 1 ² = 97% 2.4% 3.0% 5.4% 3.7% 2.9% 2.9% 2.9% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 2.9% 3.0% 3.0% 3.0% 3.0% 3.0% 3.0% 3.0% 3.0	1.80 [1.65, 1.95] 0.00 [-0.40, 0.40] 0.30 [-1.28, 1.88] 0.30 [-1.28, 1.88] 0.00 [-0.38, 0.38] -1.14 [-1.29, -0.99] -2.93 [-4.79, -1.07] -0.12 [-0.39, 0.15] -0.51 [-1.23, 0.21] -1.70 [-2.87, -0.53] 0.00 [-0.18, 0.18] -0.75 [-2.40, 0.91] -2.43 [-2.79, -2.07] -0.80 [-1.89, 0.29] 0.10 [-0.17, 0.37] 0.80 [-0.17, 1.77] -0.20 [-0.46, 0.06] -1.64 [-1.79, -1.49] 0.00 [-0.36, 0.36] -0.18 [-0.41, 0.05] 0.00 [-0.14, 0.14]	
Lee 2012 Neuts 2018 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.7 12 h Li 2020 Neuts 2018 Pani 2019 Saini 2021 Waleed 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.8 16 h Lee 2012 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 1.1.9 1 d Dhir 2016 Lee 2012 Li 2020 Liu 2020 Neuts 2018 Pani 2019 Neuts 2018 Pani 2019 Neuts 2018 Pani 2021 Waleed 2016 Zanfaly 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect	$1.9 \\ 4$ = 1.78; C z.45; 3 3.98; 1 3.27 = 0.58; C t: Z = 1.3 3.1 4 = 1.26; C t: Z = 0.8 3.92; 3.1 3.18; 3.9 2.96; 0.36; 3.07; 6 = 0.84; C	$\begin{array}{l} 0.53\\ 0.25\\ hi^2 = 8 \\ 7 \ (P = (\\ 0.55\\ 0.79\\ 0.32\\ 1.55\\ 0.5\\ 0.5\\ 0.5\\ hi^2 = 1\\ 9 \ (P = (\\ 0.25\\ hi^2 = 7.\\ 9 \ (P = (\\ 0.7\\ 1.6\\ 0.64\\ 1.7\\ 0.73\\ 0.31\\ 0.77\\ 0.43\\ 0.25\\ hi^2 = 4\\ 8 \ (P = (\\ 0.25\\ 0.5)\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ 0.5$	48 255 91 0.79, d 40 48 35 30 188 16.98, 0.17) 18 8 25 43 93, df 0.38) 27 18 8 40 0 28 5 53 5 52 78 16.97, 0.11)	$\begin{array}{c} 0.1 \\ 4 \\ \end{array}$	0.06 1 0.58 1.1 0.35 5.41 0.55 (P < 0.0 1.7 0.375 = 0.005 0.6 2.1 0.57 1.4 0.59 0.35 0.77 0.47 0.25	50 25 101 0001); F 60 50 37 35 50 192 00001); F 26 23 26 40 20 50 37 35 51 286 40 25 50 27 286 90001);	$\begin{array}{c} 3.0\%\\ 2.9\%\\ 8.0\%\\ 2 = 98\%\\ \end{array}$ $\begin{array}{c} 3.0\%\\ 2.9\%\\ 3.0\%\\ 1.8\%\\ 3.0\%\\ 13.6\%\\ 1^2 = 97\%\\ \end{array}$ $\begin{array}{c} 2.4\%\\ 3.0\%\\ 5.4\%\\ 3.0\%\\ 2.5\%\\ 3.0\%\\ 2.9\%\\ 3.0\%\\ 3.0\%\\ 2.9\%\\ 3.0\%\\ 2.9\%\\ 3.0\%\\ 2.9\%\\ 3.0\%\\ 2.9\%\\ 3.0\%\\ 3.0\%\\ 2.9\%\\ 3.0\%\\ 3.0\%\\ 2.9\%\\ 3.0\%\\ 3.0\%\\ 2.9\%\\ 3.0\%\\ 3.0\%\\ 2.9\%\\ 3.0\%$	$\begin{array}{c} 1.80 \ [1.65, \ 1.95]\\ 0.00 \ [-0.40, \ 0.40]\\ 0.30 \ [-1.28, \ 1.88]\\ \end{array}$	
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Figure 4. A forest plot diagram showing VAS or NRS The pooled results showed that ISB group had lower VAS or NRS in PACU (MD = 1.38, 95% CI [0.16,2.60], P=.03),4 h after operation (MD = 1.78, 95% CI [0.72,2.85], P=.001). and 6 h after operation (MD = 1.08, 95% CI [0.40, 1.76], P=.002). No significant difference was found for VAS or NRS 8 h after operation(MD=0.3, 95% CI [-1.28,1.88], P=.71),12 h (MD=-0.51, 95% CI [-1.23,0.21], P=.17), 16 h (MD=-0.75, 95% CI [-2.4,0.91], P=.38)and 1d after operation((MD=-0.5, 95% CI [-1.13,0.12], P=.11) between two groups.

Charles C. L	SSNB+A		ISB	-		Risk Ratio	Risk Ratio
Study or Subgroup 1.2.1 Numb/Tingling	Events 1	Iotal	Events	Fotal	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
, 3 3	2	27	2	22	4 00/	0 57 [0 10 2 11]	
Dhir 2016	2	27 40	3	23	4.0%	0.57 [0.10, 3.11]	
Li 2020 Luo 2019	2 3	20	8 13	40 20	4.7% 6.2%	0.25 [0.06, 1.11] 0.23 [0.08, 0.69]	
Zanfaly 2015	0	20	13	25	1.7%	0.33 [0.01, 7.81]	
Subtotal (95% CI)	0	112	1	108	16.5%	0.29 [0.13, 0.61]	
Total events	7		25				•
Heterogeneity: $Tau^2 = Test$ for overall effect:	0.00; Chi ²		81, df =	3 (P =	0.85); l ² =	= 0%	
1.2.3 Weakness							
Dhir 2016	3	27	7	23	5.6%	0.37 [0.11, 1.25]	
Li 2020	1	40	18	40	3.4%	0.06 [0.01, 0.40]	·
Pani 2019	2	35	37	37	5.7%	0.07 [0.02, 0.23]	
Saini 2021	0	35	5	35	1.9%	0.09 [0.01, 1.58]	
Waleed 2016 Zanfaly 2015	0 0	30 25	16 7	30 25	2.0% 2.0%	0.03 [0.00, 0.48] 0.07 [0.00, 1.11]	
Subtotal (95% CI)	0	192	/	190	2.0% 20.7%	0.11 [0.05, 0.24]	
Total events	6		90		/0		-
Heterogeneity: Tau ² = Test for overall effect:	0.21; Chi ²		18, df =	5 (P =	0.29); I ² =	= 19%	
1.2.4 Horner syndrom	ie						
Li 2020	0	40	10	40	2.0%	0.05 [0.00, 0.79]	·
Pani 2019	0	35	1	37	1.6%	0.35 [0.01, 8.36]	
Waleed 2016	0	30	5	30	1.9%	0.09 [0.01, 1.57]	·
Zanfaly 2015	0	25	9	25	2.0%	0.05 [0.00, 0.86]	
Subtotal (95% CI)		130		132	7.6%	0.09 [0.02, 0.37]	
Total events	0		25		*		
Heterogeneity: Tau ² = Test for overall effect:				3 (P = 1	0.78); l ² =	= 0%	
1.2.5 Subjective dysp			_				
Li 2020	0	40	7	40	2.0%	0.07 [0.00, 1.13]	• • • • • • • • • • • • • • • • • • • •
Neuts 2018	0	48	1	50	1.6%	0.35 [0.01, 8.31]	
Pani 2019 Walcod 2016	2 0	35 30	8	37	4.7%	0.26 [0.06, 1.16]	
Waleed 2016 Zanfaly 2015	0	25	4 2	30 25	1.9% 1.8%	0.11 [0.01, 1.98] 0.20 [0.01, 3.97]	· · · ·
Subtotal (95% CI)	0	178	2	182	12.0%	0.19 [0.07, 0.55]	
Total events	2		22			0120 [0101, 0100]	
Heterogeneity: $Tau^2 = Test$ for overall effect:	0.00; Chi ²		04, df =	4 (P =	0.90); l ² =	= 0%	
1.2.6 Hoarseness							
Li 2020	0	40	9	40	2.0%	0.05 [0.00, 0.87]	· · · · · · · · · · · · · · · · · · ·
Pani 2019	5	35	7	37	6.3%	0.76 [0.26, 2.16]	
Waleed 2016	0	30	4	30	1.9%	0.11 [0.01, 1.98]	
Zanfaly 2015	0	25	2	25	1.8%	0.20 [0.01, 3.97]	
Subtotal (95% CI)	-	130	22	132	12.1%	0.26 [0.06, 1.12]	
Total events Heterogeneity: Tau ² = Test for overall effect:				3 (P =	0.16); I ² =	= 42%	
1.2.7 Nausea/Vomitin	-				_		
Dhir 2016	7	27	13	23	7.8%	0.46 [0.22, 0.95]	
Li 2020	4	40	2	40	4.2%	2.00 [0.39, 10.31]	
Luo 2019	1	20	2	20	2.7%	0.50 [0.05, 5.08]	
Pani 2019	4	35	2	37	4.2%	2.11 [0.41, 10.83]	
Pitombo 2013	4	34	6	34	5.8%	0.67 [0.21, 2.15]	
Waleed 2016	4	30	2	30	4.3%	2.00 [0.40, 10.11]	
Zanfaly 2015 Subtotal (95% CI)	1	25 211	1	25 209	2.1% 31.1%	1.00 [0.07, 15.12] 0.80 [0.47, 1.36]	
Total events Heterogeneity: Tau ² = Test for overall effect:		² = 6.4					
Total (95% CI) Total events	45	953	212	953	100.0%	0.29 [0.19, 0.46]	•
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diffe	0.52; Chi ² Z = 5.39 ((P < 0	.50, df = .00001)				0.01 0.1 1 10 100 SSNB+ANB ISB

Figure 5. A forest plot diagram showing Block related complications. The pooled data showed that SSNB+ ANB group had lower incidence of numb/tingling (RR = 0.29, 95% CI [0.13,0.61], P=.001), weakness (RR=0.11, 95% CI [0.05,0.24], P <.0001), Horner syndrome (RR=0.09, 95% CI [0.02,0.37], P=.001) and Subjective dyspnea (RR=0.19, 95% CI [0.07,0.55], P=.002). No significant difference was found for Hoarseness (RR=0.26, 95% CI [0.06,1.12], P=.07), and nausea/vomiting (RR=0.8, 95% CI [0.47,1.36], P=.41).

	SSN	IB+AN	В		ISB			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.3.2 Patient Satisfac	tion								
Dhir 2016	7.9	2.4	27	8.6	2.3	23	16.4%	-0.70 [-2.01, 0.61]	
Lee 2012	7.6	1.2	18	7.2	2	26	22.7%	0.40 [-0.55, 1.35]	
Li 2020	9.33	0.94	40	8.35	1.25	40	33.3%	0.98 [0.50, 1.46]	
Pitombo 2013	9.21	1.53	34	9.2	1.53	34	27.6%	0.01 [-0.72, 0.74]	+
Subtotal (95% CI)			119			123	100.0%	0.31 [-0.38, 0.99]	
Heterogeneity: Tau ² =	• 0.31; 0	Chi² =	8.76, d	lf = 3 (I	P = 0.0)3); I ² =	= 66%		
Test for overall effect	: Z = 0.8	87 (P =	= 0.38)						
Total (95% CI)			119			123	100.0%	0.31 [-0.38, 0.99]	
Heterogeneity: Tau ² =	= 0.31; (Chi ² =	8.76, d	lf = 3 (I	P = 0.0)3); l ² =	= 66%		
Test for overall effect	: Z = 0.8	87 (P =	= 0.38)						-2 -1 0 1 2 SSNB+ANB ISB
Test for subgroup dif	ferences	Not :	annlical	hle					SSIND+AIND ISD

Figure 6. A forest plot diagram showing patient satisfaction. We didn't find any significant difference for patient satisfaction MD=0.31, 95% CI [-0.38,0.99], P=.38).

In our study, SSNB+ANB provided inadequate analgesia to ISB in the immediate postoperative period at PACU,4 hours, and 6 hours. The analgesic difference between the two groups gradually decreased as the blocks wore off, and pain scores became comparable during the 12 hours, 16 hours, and 1 day after surgery between SSNB+ANB and ISB groups. There are several reasons for increased pain in the SSNB+ANB group in the immediate postoperative period. First, irrigation fluid from the arthroscopic procedure may take up to 12 hours to be absorbed; Second, capsular overdistension may contribute to the increased pain in the SSNB+ANB group. Third, the subscapular muscles, the acromioclavicular articulation, and the anterior portion of the glenohumeral articular capsule are not supplied by the SSNB +ANB technique. Fourth, The suprascapular nerve's superior articular branch may leave the nerve before entering the suprascapular fossa.^[20]

In our meta-analysis, the incidence of numb/tingling, weakness, Horner syndrome, and subjective dyspnea was higher and statistically significant in the ISB group compared with the SSNB + ANB group. Interscalene block causes a motor blockade of muscles supplied by the brachial plexus, resulting in weakness extending to the forearm and hand. The radial, median, musculocutaneous, and ulnar nerves receive contributions from C7-T1 nerve roots. As the ISB technique is most often done at the level of C5-C6, the ISB may spare the lower segments (C7-T1) of the brachial plexus,^[21] so the patients may be present with numb or tingling. Urmey et al. reported all patients undergoing ISB had the complication of phrenic nerve block, which may be due to the unpredictable local anesthetic spread to adjacent structures like neural structures or the stellate ganglion.^[22] The patients may present with Horner syndrome and Subjective dyspnea.

The present study showed a good patient satisfaction level in both the SSNB+ANB group and the ISB group. Motor blockade associated with an SSNB and AXNB is confined to the deltoid, supraspinatus, infraspinatus, and teres minor muscles (posterior rotator cuff). The outer pectoral girdle muscles such as latissimus dorsi and pectoral are preserved and those of the hand, forearm, and upper arm. Thus, in addition to provide analgesia, the SSNB +ANB technique provides potential conservation of the patient's functional capacity to improve patient satisfaction.

Management of arthroscopic shoulder surgery pain is often accomplished by using opioids; however, their use is often associated with side effects such as vomiting, nausea, dysphoria, respiratory depression, and hormonal effects.^[23,24] Our findings may have an impact on clinical practice. The minor analgesic advantages of ISB compared with the SSNB +ANB seem to be transient and limited to the immediate postoperative period (before 6 hours after the operation). In contrast, the risk of block-related complications associated with ISB may outweigh its benefits in specific settings or patient populations, especially when SSNB can offer a safe and effective alternative in patients with the severe chronic obstructive pulmonary disease,^[7,25] obstructive sleep apnea,^[26] contralateral phrenic nerve and morbid obesity.^[27] Our findings established the SSNB+ANB's clinical benefits as an attractive, effective treatment for postoperative pain in patients undergoing arthroscopic shoulder surgery.

4.1. Limitations

Our meta-analysis has limitations that should be acknowledged. First, heterogeneity was found across the included studies in terms of standardization in nerve block techniques, the dose of anesthetic, type of shoulder surgeries performed as well as the timing of assessment, which precluded the pooling of many of outcomes. Second, some studies included in this review had smaller sample sizes, which may decrease the strength of their effect and limit external validity. Third, we didn't evaluate the total opioid consumption because it's hard to calculate the total opioid consumption in these studies. Another bias inherent to the present study relates to the inability to blind the operator to the block technique being performed because of the interventions' nature.

5. Conclusion

ISB seems to offer analgesic advantages that are transient and limited to 6 hours after the operation. SSNB + ANB is not different from ISB concerning postoperative pain severity between 6 hours to the first 24 hours postoperation. Furthermore, SSNB + ANB does appear to reduce the risk of numb/tingling, weakness, Horner syndrome, and Subjective dyspnea. Our high-level evidence has established SSNB + ANB as an effective and safe analgesic technique and a clinically attractive alternative to ISB during arthroscopic shoulder surgery, especially for patients of severe chronic obstructive pulmonary disease, obstructive sleep apnea, contralateral phrenic nerve, and morbid obesity. Given our meta-analysis's relevant possible biases, we required more adequately powered and better-designed RCT studies with longterm follow-up to reach a firmer conclusion.

Author contributions

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Methodology: Huadong Yang.

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Resources: Xiaofei Zhang.

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Visualization: Huadong Yang.

Writing – original draft: Changjiao Sun.

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