

Ilioinguinal/iliohypogastric nerve block versus transversus abdominis plane block for pain management following inguinal hernia repair surgery

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Controversy still exists regarding the efficiency and safety of ilioinguinal/iliohypogastric nerve (II/IH) block versus transversus abdominis plane (TAP) block for pain management after inguinal hernia repair. The purpose of the current meta-analysis was to perform a relatively credible and comprehensive assessment to compare the efficiency and safety of II/IH versus TAP for pain management after inguinal hernia repair.

Methods: The PUBMED, CENTRAL, and EMBASE were systematically searched. Studies comparing II/IH versus TAP for pain management in adult patients undergoing inguinal herniorrhaphy were included. The results of this study are synthesized and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Results: Six studies with 632 patients were included in this study. No statistically significant difference was observed between the II/ IH and TAP groups in postoperative opioid use, the time to first request for rescue analgesia, the incidence of postoperative nausea and vomiting (PONV), incidence of complication related with nerve blocks and patient satisfaction. The TAP group had a significantly higher pain score at 6 and 8 hours postoperatively (6 hours: mean difference [MD] = 0.94, 95% confidence interval [CI] 0.67-1.22, $l^2 = 0\%$, P < .01; 8 hours: MD = 1.02, 95% CI 0.3-1.74, $l^2 = 59\%$, P < .01). However, no statistically significant difference was observed at 1, 2, 4, 12, 24, 48 hours, and 6 months postoperatively.

Conclusions: In general, this meta-analysis revealed that both approaches have similar postoperative opioid consumption and no significant difference in postoperative complication and patient satisfaction. The II/IH block provides excellent analgesic effects at 6 and 8 hours after inguinal herniorrhaphy in compared with the TAP block. However, more high-quality randomized controlled trials with long-term follow-up are still required to make the conclusion.

Abbreviations: CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation, II/ IH = Ilioinguinal/iliohypogastric nerve block, MD = mean difference, PONV = postoperative nausea and vomiting, RR = risk ratios, SD = standard deviation, TAP = transversus abdominis plane block, USG = ultrasonic guided.

Keywords: inguinal hernia, meta-analysis, nerve block

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The authors have no conflicts of interest to disclose.

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1. Introduction

Repair of inguinal hernia is one of the most commonly performed procedures with most of them being performed on a day surgery center.^[1] Though not a very extensive surgery, inguinal hernia repair is reported to be associated with about 60% incidence of moderate to severe postoperative pain.^[2] Moreover, 0% to 54% of this acute postoperative pain develops into chronic pain.^[3] Incisional pain is an essential part of post-hernia surgery pain, and various medications and non-pharmacological techniques have been adopted for postoperative analgesia.^[4] However, an optimal pain management technique is still undetermined.

Recently, ilioinguinal/iliohypogastric (II/IH) nerve block and transversus abdominis plane (TAP) block are getting more and more attention as viable alternatives to provide effective perioperative analgesia for inguinal surgery.^[5,6] Both TAP and II/IH produce the same block of the ilioinguinal and iliohypogastric nerves. The only difference is that TAP is a compartment block, while II/IH blocks the truncal. Ultrasonic-guided (USG) TAP block was found to be superior to landmark-guided, but inferior to USG II/IH block in open inguinal hernia repair in a systematic review which evaluated the analgesic effect of TAP block in various abdominal operations.^[7] However, the above result was derived from just 2 studies in the previous systematic review. A growing number of studies have compared these 2 techniques in analgesia for inguinal repair with variable outcomes. TAP block was reported to provide better or at least comparable postoperative analgesia in adult patients undergoing inguinal hernia repair.[8-10] However, an increasing number of studies have shown that II/IH block provided better pain control than TAP block following the inguinal hernia repair both in children and adults.[11-13]

To reconcile these conclusions, we conducted this meta-analysis and systematic review to summarize the current evidence and compare the analgesic efficacy and side effects of II/IH block versus TAP block in adult patients undergoing inguinal hernia repair.

2. Methods

The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement in this study,^[14] and ethical approval was not necessary.

2.1. Search strategy

A systematic and comprehensive search was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), PUBMED, and EMBASE from database established to February 1, 2019, without language limitation. The search strategy included the following terms: "ilioinguinal," "iliohypogastric," "local anesthesia," "local anesthetics," "bupivacaine," "lignocaine," "IIN/IHN," "transversus abdominis plane," "TAP," "inguinal canal," "hernia," and "inguinal hernia." The results of this search strategy were limited to randomized controlled trials and humans. Moreover, the reference lists of included articles were manually scrutinized for any relevant trials not identified using the strategy described above.

2.2. Study selection

We identified randomized controlled trials comparing TAP block with II/IH block for postoperative analgesia in adult patients undergoing inguinal hernia repair. Studies were included no matter the blocks were performed by landmark-based or ultrasound-guided (USG) techniques in the perioperative period. Patients might underwent inguinal hernia repair under spinal or general anesthesia in the included studies. Studies were excluded if they utilized catheter-based TAP blocks, adopted different analgesic adjuvants or different long-acting intrathecal opioids within the 2 study groups.

Moreover, if 1 of the 2 interventions was combined with another analgesia method (e.g., wound infiltration), the study was also excluded. Retrieved studies were imported into Endnote (version X7; Thomson Reuters), where duplications were detected and deleted automatically. Two authors independently scanned the titles and abstract of retrieved studies according to the established eligibility criteria to exclude the apparent irrelevant studies. The full-text was further evaluated if the judgement could not quickly be decided based on its title or abstract. A third reviewer settled any disagreements between reviewers.

2.3. Data extraction

The data of included studies were independently extracted by 2 reviewers using a standardized datasheet. The following data were extracted: the author, year of publication, study location, types of surgery, types of anesthesia, sample size, average ages of participants, details of interventions, the timing of nerve block, outcomes, and the adverse events. The corresponding authors of studies were tried to be contacted for insufficient data. We measured the graphs if the authors failed to provide the required numerical data. When only the median and range were offered, the mean and standard deviation (SD) were estimated by the calculator with a compiled formula recommended by Luo et al.^[15]

2.4. Quality assessment

The Cochrane risk of bias tool, which is recommended by the Cochrane Collaboration for risk of bias assessment, was used in this study.^[16] There are 7 domains in the Cochrane risk of bias tool, including the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The judgment of each domain is presented as "low risk," "high risk," or "unclear risk" based on the instruction of Cochrane Collaboration. To assess the quality of evidence, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method exploring the 5 different GRADE domains including study limitations, consistency of effect, imprecision, indirectness, and publication bias. Two reviewers performed the above assessments with disagreement settled by a third reviewer.

2.5. Study outcome

The primary outcome was the difference in cumulative 24 hours intravenous opioid consumption (in milligram morphine equivalents) between the TAP and II/IH block groups. The secondary outcomes were VAS scores at rest 1, 2, 4, 6, 8, 12, 24, 48 hours, and 6 months post-procedure, the time to first request for rescue analgesia, the incidence of postoperative nausea and vomiting (PONV), the incidence of complication related to nerve block (urinary retention, hematoma, hypotension, bradycardia, arrhythmia) and patient satisfaction. To standardize analysis, other opioid analgesics were converted to equivalent morphine doses by using recognized conversion ratios.^[17] The pain reported as visual, verbal, or numerical rating scales was converted to a 0- to 100-point scale (where 0 represents no pain, and 100 represents worst pain imaginable). Any reported postoperative nausea or vomiting in the included studies was treated as PONV.

2.6. Statistical methods

Data analysis was performed by the Review Manager software (RevMan, version 5.3.5; Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Risk ratios (RR) with corresponding 95% confidence interval (95% CI) was calculated for dichotomous data, and continuous data were analyzed using the mean difference (MD) with corresponding 95% CI. Heterogeneity among studies was evaluated using the I^2 statistic. If the $I^2 > 50\%$, the random-effect model was used, otherwise a fixed-effect model was used. Subgroup analysis was performed to evaluate pain score at different time points postoperatively. We excluded the studies in which nerve block was performed by landmark techniques in the sensitivity analysis to explore the heterogeneity among studies in the implementation of the nerve block. For all tests, statistical significance was defined as a P < .05.

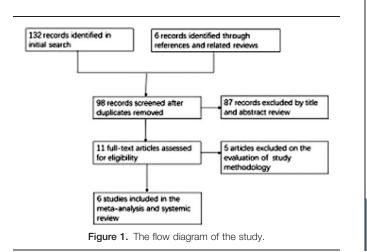
3. Results

3.1. Results of search

The initial literature search identified 138 articles from all databases, and 42 duplicate articles were excluded. Eighty-seven articles were excluded after screened titles and abstracts. And 5 articles were excluded after full-text reading for the following reasons: reviews or systematic reviews, without required outcomes, II/IH block was combined with wound infiltration. Finally, 6 RCTs met the inclusion criteria and were retained for analysis. The flow diagram of study selection is shown in Fig. 1. A total of 632 patients were included in the final analysis: 314 patients in the TAP group and 318 patients in the II/IH group. Two authors were tried to be contacted for insufficient data and 1 author responded.^[11]

3.2. Description of included studies

Characteristics of the included studies are shown in Table 1. All blocks in included studies were performed before incision except



Study ID Country											
Study ID Cou			Number pe	per Group	Αç	Age		Intervention	tion	Interventi	Intervention drugs
Study ID Cou							Intervention				
	ntry Operation	Anesthesia	TAP	HI/II	TAP	HI/II	time	TAP	HI/II	TAP	HI/II
Faiz 2019 Iran	Elective primary open unilateral inguinal herniorrhaphy	General or neuraxial anesthesia	45	45	47.6±12.8	46.4±13.8	After operation	USG mid-axillary line in umbilicus level TAP	USG I//H	0.2% bupivacaine 15 mL	0.2% bupivacaine 15 mL
Bhatia India 2019	t Elective primary, unilateral open inguinal herniorrhaphy	Subarachnoid block	25	25	54.38 ± 10.97	52.04 ± 13.27	Before incision	USG medial TAP block	USG INH	0.25% bupivacaine 0.3mL/kg	0.25% bupivacaine 0.3mL/kg
Kamal India 2018	Ele	General anesthesia	30	30	33.7±14.1	34.1 ± 13.2	Before incision	USG unilateral TAP block	USG I//H	0.75% ropivacaine 3 mg/kg	0.75% ropivacaine 10 mL
Okur Turkey 2017	Ë	Subarachnoid block	30	30	55.50 ± 16.77	49.47 ± 17.44	Before incision	USG unilateral TAP block	USG I//H	0.25% bupivacaine 20mL	0.25% bupivacaine 5 mL
Stav Israel 2016	Ē	General anesthesia	50	49	50 ± 17	46 ± 19	Before incision	USG unilateral TAP block	USG II/H	Bupivacaine 5 mg/mL with adrenaline 5 μg/mL 20 mL	Bupivacaine 5 mg/mL with adrenaline 5 µ.g/mL 20 mL
Aveline France 2010	ce Elective primary unilateral open inguinal hemiorrhaphy	General anesthesia	134	139	58±13	60±12	Before incision	USG unilateral TAP block	Conventional IVIH	0.5% lévobupivacaine 1.5 mg/kg	0.5% levobupivacaine 1.5 mg/kg

IVIH = Ilioinguinal/iliohypogastric, TAP = transversus abdominis plane, USG = ultrasound guidance.

able.

in one study,^[18] and ultrasound guidance was adopted in all nerve blocks except in the II/IH group of one study.^[8] One included study in this meta-analysis performed TAP blocks at mid-axillary line,^[18] one along the anterior axillary line,^[9] 4 did not descript the precise site of injection.^[8,10,11,13] Of the 6 included studies, 4 utilized bupivacaine,^[9,10,11,18] 1 utilized levobupivacaine,^[8] and 1 utilized ropivacaine.^[13]

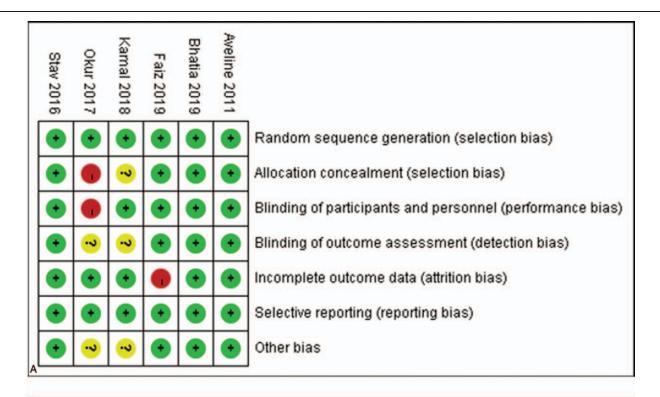
3.3. Risk of bias within studies

The risk-of-bias assessment of the included studies is summarized in Fig. 2. All included studies provide a satisfactory description of their random processes. The blinding process was at high risk of bias in 1 study^[10] and unclear risk of bias in another study^[13] due

to ambiguous description. One study had incomplete descriptions of their outcome data. $^{\left[13\right] }$

3.4. Intravenous equivalent morphine consumption at 24 hours postoperatively

All the included studies reported the additional opioid analgesic requirements at 24 hours postoperatively. One of them reported the number of patients needing rescue analgesia and showed no significant difference between study groups.^[10] Patients received tramadol in the first 4 hours after the surgery and diclofenac in 4 to 24 hours postoperatively for postoperative analgesia in another included study.^[13] The result of that study showed no significant difference in tramadol consumption between study groups. However, the average dose of diclofenac was significantly



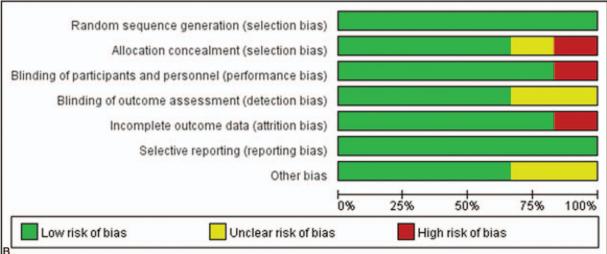
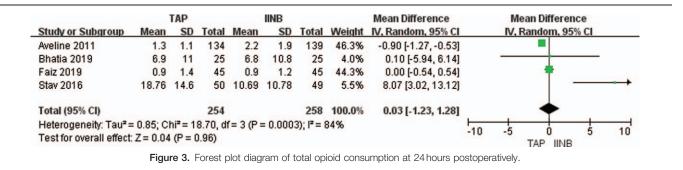


Figure 2. Quality assessment of included studies. The green circles indicate lack of bias; red circles indicate the presence of bias. A, Risk of bias for each included study. The studies were assessed for 7 types of bias and for the use of an intent-to-treat analysis. B, The overall summary of bias of the 6 studies.



higher in the TAP group than that in the II/IH group. Four trials,^[8,9,11,18] including 512 patients were eligible for metaanalysis of intravenous equivalent morphine consumption at 24 hours postoperatively. TAP block did not increase the intravenous equivalent morphine consumption significantly in comparison with the II/IH block during the first 24 hours (MD, 0.03, 95% CI -1.23 to 1.28, I^2 =84%; P=.96) (Fig. 3). Moreover, the sensitivity analysis that excluded studies in which nerve block was performed by landmark techniques further supported the above conclusion (MD, 2.46; 95% CI -2.58 to 7.50, I^2 =79%; P=.34).

3.5. Postoperative pain

Comparing TAP with II/IH, pain scores at rest 1 hour, 2 hours postoperatively were analyzed in 3 studies^[9,10,13] (TAP 84 vs II/ IH 84 patients). No significant difference was found for pain scores at these time points (1 hour: MD = -0.03, 95% CI -0.24-0.17, $I^2 = 49\%$, P = .75; 2 hours: MD = -0.32, 95% CI -0.47-1.10, $I^2 = 86\%$, P = .43). Pain scores at rest for 4 hours after procedure were analyzed in 4 studies^[8-10,13] (TAP 218 vs II/IH 223 patients) and showed no significant difference (MD = -0.11, 95% CI -0.84 to 1.07, $I^2 = 95\%$, P = .82). Pain scores at rest 6 hours, 8 hours postoperatively were analyzed in 2 studies. The meta-analysis suggested that patients who underwent TAP block had higher pain scores at 6 and 8 hours than patients who underwent II/IH block (6 hours: MD = 0.94, 95% CI 0.67-1.22, $I^2 = 0\%$, P < .01; 8 hours: MD = 1.02, 95% CI 0.3-1.74, $I^2 =$ 59%, P < .01). Two studies (TAP 158 vs II/IH 163 patients) reported pain scores at rest 12 hours postoperatively, with no significant difference (MD = -0.3, 95% CI $-1.36-0.77, I^2 = 97\%$, P=.59). Pain scores at rest for 24 hours postoperatively were analyzed in 5 studies^[8-11,13] (TAP 268 vs II/IH 272 patients) and showed no significant difference (MD=-0.46, 95% CI -1.29 to 0.37, $I^2 = 93\%$, P = .28). Two studies (TAP 164 vs II/IH 169 patients) reported pain scores at rest 48 hours postoperatively, with no significant difference (MD = -0.06, 95% CI -0.26-0.13, $I^2 = 0\%$, P = .52). The overall effect of meta-analysis showed no significant difference in postoperative pain scores at rest between TAP group and II/IH group (MD = 0.1, 95% CI – 0.18–0.38, I^2 = 93%, P=.5) (Fig. 4). In addition, the result of sensitivity analysis was consistent with the above results (MD = 0.24,95% CI -0.07- $0.55, I^2 = 91\%, P = .12$).

3.6. Chronic pain

Only 2 studies reported chronic pain scores after the procedure. One study^[8] including 273 participants (TAP 174 vs II/IH179 patients) showed that there was no significant difference in pain scores at rest and movement 3 and 6 months after surgery. Another study,^[10] which included 30 patients in each group showed comparable pain scores at 1 month and 6 months postoperatively. The meta-analysis of pain scores at 6 months did not show a significant difference between TAP group and II/IH group neither (MD=-0.17, 95% CI -0.46-0.12, I^2 =0%, P=.25) (Fig. 5). Sensitivity analysis could not be conducted because only 1 study left after exclusion of study in which nerve was performed by landmark technique.

3.7. Time to the first request for rescue analgesic

One hundred seventy patients were analyzed from 3 RCTs^[9,10,13] regarding the time to first request for rescue analgesia with 85 patients in the TAP group and 85 patients in the II/IH group. There were no significant differences between both groups regarding the time to first request for rescue analgesia (MD, – 52.95, 95% CI –152.33–46.43, I^2 =73%; P=.3) (Fig. 6). No sensitivity analysis was conducted due to none of the included studies were eligible for exclusion.

3.8. Incidence of PONV at 24 hours postoperatively

The data of PONV at 24 hours postoperatively were reported in 6 studies,^[8–11,13,18] including 632 patients in all. One study^[9] including 50 participants reported no patient from either group experienced nausea or vomiting. Therefore, 582 patients from 5 studies were included in the meta-analysis at last. The result of the meta-analysis showed that there is no significant difference in PONV at 24 hours postoperatively between the TAP group and the II/IH group (RR = 1.08; 95% CI 0.59–1.99, I^2 =0%; *P*=.80) (Fig. 7). Moreover, the sensitivity analysis further strengthened the above conclusion (TAP 180 vs II/IH 179 patients, RR = 2.14; 95% CI 0.61–7.47, I^2 =0%; *P*=.23).

3.9. Incidence of complication associated with the nerve block

There were 5 trials^[8–11,13] that reported the incidence of complication related to the nerve block, with a total of 542 participants. Two studies,^[9,11] including 149 participants, reported no patient from either group experienced complication related with the nerve block. The meta-analysis of the remaining 393 patients suggested that the TAP block did not significantly decrease the incidence of complication which is related to the nerve block in comparison with the II/IH block (RR = 1.01; 95% CI 0.35–2.86, I^2 =0%; P=.80) (Fig. 8). In addition, the sensitivity analysis did not change the above conclusion (RR = 1.15; 95% CI 0.44–3.06, I^2 =46%; P=.77).

Study or Subgroup		TAP	Total		IINB	Total	Moight	Mean Difference	Mean Difference
1.1.1 1h	mean	SD	Total	mean	SU	Total	vvelgnt	IV, Random, 95% CI	IV, Random, 95% CI
	0.26	0.26	24	0.6	0.66	24	5.0%	0.251.052.0.021	-
3hatia 2019 Kamal 2018		0.26	24 30		0.65	24 30	5.0% 5.1%	-0.25 [-0.53, 0.03] 0.12 [-0.12, 0.36]	+
Okur 2017		0.53	30		0.42	30	5.1%		_
Subtotal (95% CI)	0.5	0.49	84	0.5	0.49	84	15.2%	0.00 [-0.25, 0.25]	•
Heterogeneity: Tau ² =	0.02.0	hi2 - 2		- 2 /P -	0 1 11			-0.05 [-0.24, 0.17]	1
Fest for overall effect:				· 2 (F =	0.14),	1 - 48	70		
1.1.2 2h									
Bhatia 2019	0.5	0.65	24	0.88	1.17	24	4.4%	-0.38 [-0.92, 0.16]	
Kamal 2018	1.6	0.62	30	0.8	0.58	30	5.0%	0.80 [0.50, 1.10]	
Okur 2017	2.25	1.72	30	1.75	1.23	30	3.8%	0.50 [-0.26, 1.26]	
Subtotal (95% CI)			84			84	13.2%	0.32 [-0.47, 1.10]	-
+eterogeneity: Tau² = fest for overall effect:				'= 2 (P	= 0.00	09); I² =	86%		
1.1.3 4h									
Aveline 2011	1.07	1.27	134	1.57	0.91	139	5.0%	-0.50 [-0.76, -0.24]	-
Bhatia 2019		1.57	24		1.95	24	3.2%	-0.37 [-1.37, 0.63]	
Kamal 2018		0.48	30		0.65	30	5.0%	0.99 [0.70, 1.28]	
Okur 2017		1.72	30		1.47	30	3.7%	0.25 [-0.56, 1.06]	<u> </u>
Subtotal (95% CI)			218	-		223	16.9%	0.11 [-0.84, 1.07]	+
Heterogeneity: Tau² = Test for overall effect:				'= 3 (P	< 0.00	001); I ²	= 95%		
1.1.4 6h									
Kamal 2018		0.49	30		0.68	30	5.0%	0.98 [0.68, 1.28]	
Okur 2017	2.5	1.47	30	1.75	1.23	30	4.0%	0.75 [0.06, 1.44]	
Subtotal (95% CI)			60			60	9.0%	0.94 [0.67, 1.22]	
Heterogeneity: Tau² = Fest for overall effect:					0.55);	I ² = 0%			
1.1.5 8h									
Bhatia 2019	2.13	1.43	24	1.63	1.82	24	3.4%	0.50 [-0.43, 1.43]	-+
Kamal 2018		0.45	30		0.71	30	5.0%	1.28 [0.98, 1.58]	
					0.71	30 54			•
Subtotal (95% Cl) Heterogeneity: Tau² =	3.35 = 0.18; C	0.45 hi² = 2	30 54 .47, df=	2.07		54	5.0% 8.3%	1.28 [0.98, 1.58]	•
Subtotal (95% Cl) Heterogeneity: Tau² = Fest for overall effect:	3.35 0.18; C	0.45 hi² = 2	30 54 .47, df=	2.07		54	5.0% 8.3%	1.28 [0.98, 1.58]	•
Subtotal (95% Cl) Heterogeneity: Tau² = Fest for overall effect: 1.1.6 12h	3.35 = 0.18; C Z = 2.76	0.45 hi² = 2 6 (P = 0	30 54 .47, df=).006)	2.07 = 1 (P =	0.12);	54 I² = 599	5.0% 8.3% %	1.28 [0.98, 1.58] 1.02 [0.30, 1.74]	-
Subtotal (95% Cl) Heterogeneity: Tau² = Fest for overall effect: I.1.6 12h Weline 2011	3.35 = 0.18; C Z = 2.76 2.14	0.45 hi² = 2 6 (P = (1.34	30 54 .47, df=).006) 134	2.07 = 1 (P = 2.98	0.12); 0.95	54 ² = 599 139	5.0% 8.3% % 5.0%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56]	-
Subtotal (95% Cl) Heterogeneity: Tau ² = Fest for overall effect: I.1.6 12h Aveline 2011 Shatia 2019	3.35 = 0.18; C Z = 2.76 2.14	0.45 hi² = 2 6 (P = 0	30 54 .47, df=).006)	2.07 = 1 (P = 2.98	0.12);	54 I² = 599	5.0% 8.3% %	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53]	-
Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.1.6 12h Aveline 2011 Shatia 2019 Subtotal (95% CI) Heterogeneity: Tau ² =	3.35 = 0.18; C Z = 2.76 2.14 0.75 = 0.57; C	0.45 hi ² = 2 5 (P = 0 1.34 0.65 hi ² = 2	30 54 .47, df= 0.006) 134 24 158 9.63, df	2.07 = 1 (P = 2.98 0.5	0.12); 0.95 0.25	54 I ² = 599 139 24 163	5.0% 8.3% % 5.0% 5.0% 10.0%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56]	-
Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: 1.1.6 12h Aveline 2011 Shatia 2019 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: 1.1.7 24h	3.35 = 0.18; C Z = 2.76 2.14 0.75 = 0.57; C Z = 0.54	0.45 hi ² = 2 5 (P = (1.34 0.65 hi ² = 2 4 (P = (30 54 .47, df= 0.006) 134 24 158 9.63, df 0.59)	2.07 = 1 (P = 2.98 0.5 '= 1 (P	0.12); 0.95 0.25 < 0.00	54 ² = 599 139 24 163 001); ²	5.0% 8.3% 5.0% 5.0% 10.0% = 97%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77]	-
Subtotal (95% CI) Heterogeneity: Tau ² = rest for overall effect: .1.6 12h Weline 2011 Shatia 2019 Subtotal (95% CI) Heterogeneity: Tau ² = rest for overall effect: .1.7 24h Weline 2011	3.35 0.18; C Z = 2.76 2.14 0.75 0.57; C Z = 0.54 2.87	0.45 hi ² = 2 5 (P = (1.34 0.65 hi ² = 2 4 (P = (0.82	30 54 .47, df= 0.006) 134 24 158 9.63, df 0.59) 134	2.07 = 1 (P = 2.98 0.5 7 = 1 (P 3.24	0.12); 0.95 0.25 < 0.00 0.62	54 ² = 599 139 24 163 001); ² 139	5.0% 8.3% % 5.0% 5.0% 10.0%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20]	-
Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: 1.1.6 12h Weline 2011 Shatia 2019 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: 1.1.7 24h Weline 2011 Shatia 2019	3.35 0.18; C Z = 2.76 2.14 0.75 0.57; C Z = 0.54 2.87 0	0.45 hi ² = 2 6 (P = 0 1.34 0.65 hi ² = 2 4 (P = 0 0.82 0	30 54 .47, df= 0.006) 134 24 158 9.63, df 0.59) 134 24	2.07 = 1 (P = 2.98 0.5 7 = 1 (P 3.24 0.13	0.12); 0.95 0.25 < 0.00 0.62 0.13	54 ² = 599 24 163 001); ² 139 24	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable	-
Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: I.1.6 12h Weline 2011 Shatia 2019 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: I.1.7 24h Weline 2011 Shatia 2019 Kamal 2018	3.35 0.18; C Z = 2.76 2.14 0.75 0.57; C Z = 0.54 2.87 0 3.87	0.45 $hi^2 = 2$ 6 (P = 0 1.34 0.65 $hi^2 = 2$ 4 (P = 0 0.82 0 0.81	30 54 .47, df= 0.006) 134 24 158 9.63, df 0.59) 134 24 30	2.07 = 1 (P = 2.98 0.5 7 = 1 (P 3.24 0.13 3.74	0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88	54 ² = 599 24 163 001); ² 139 24 30	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2% 4.7%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56]	-
Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: 1.1.6 12h Weline 2011 Subtotal 2019 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: 1.1.7 24h Weline 2011 Shatia 2019 Camal 2018 Okur 2017	3.35 0.18; C Z = 2.76 2.14 0.75 0.57; C Z = 0.54 2.87 0 3.87 0.5	0.45 $hi^{2} = 2$ 5 (P = 0 1.34 0.65 $hi^{2} = 2$ 4 (P = 0 0.82 0 0.81 0.49	30 54 .47, df= 0.006) 134 24 158 9.63, df 0.59) 134 24 30 30	2.07 = 1 (P = 2.98 0.5 7 = 1 (P 3.24 0.13 3.74 2.5	0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88 1.47	54 ² = 599 24 163 001); ² 139 24 30 30	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2% 4.7% 4.4%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45]	-
Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: 1.1.6 12h Aveline 2011 Shatia 2019 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: 1.1.7 24h Aveline 2011 Shatia 2019 Atamal 2018 Okur 2017 Stav 2016	3.35 0.18; C Z = 2.76 2.14 0.75 0.57; C Z = 0.54 2.87 0 3.87 0.5	0.45 $hi^2 = 2$ 6 (P = 0 1.34 0.65 $hi^2 = 2$ 4 (P = 0 0.82 0 0.81	30 54 .47, df= 0.006) 134 24 158 9.63, df 0.59) 134 24 30 30 50	2.07 = 1 (P = 2.98 0.5 7 = 1 (P 3.24 0.13 3.74	0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88	54 ² = 599 24 163 001); ² 139 24 30 30 49	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2% 4.7% 4.4% 3.1%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45] 0.60 [-0.45, 1.65]	
Subtotal (95% CI) Heterogeneity: Tau ² = fest for overall effect: .1.6 12h Weline 2011 Shatia 2019 Subtotal (95% CI) Heterogeneity: Tau ² = fest for overall effect: .1.7 24h Weline 2011 Shatia 2019 Kamal 2018 Dokur 2017 Stav 2016 Subtotal (95% CI)	3.35 2.14; C 2.276 2.14 0.75 2.0.57; C 2.87 0.57 3.87 0.5 3.7	0.45 hi ² = 2 6 (P = (1.34 0.65 hi ² = 2 4 (P = (0.82 0 0.81 0.49 2.8	30 54 .47, df= 0.006) 134 24 158 9.63, df 0.59) 134 24 24 30 30 50 268	2.07 = 1 (P = 2.98 0.5 7 = 1 (P 3.24 0.13 3.74 2.5 3.1	0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88 1.47 2.5	54 ² = 599 24 163 001); ² 139 24 30 30 49 272	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2% 4.7% 4.4% 3.1% 17.3%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45]	
Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: 1.1.6 12h Aveline 2011 Bhatia 2019 Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: 1.1.7 24h Aveline 2011 Bhatia 2019 Kamal 2018 Okur 2017 Stav 2016 Subtotal (95% CI) Heterogeneily: Tau ² =	3.35 2.14 0.75 2.14 0.75 2.0.57; C 2.87 0 3.87 0.5 3.7 2.5 3.7	0.45 $hi^2 = 2$ $\delta (P = 0$ 1.34 0.65 $hi^2 = 2$ 0 0.81 0.49 2.8 $hi^2 = 4$	30 54 .47, df= 0.006) 134 24 158 9.63, df 0.59) 134 24 30 50 268 1.50, df	2.07 = 1 (P = 2.98 0.5 7 = 1 (P 3.24 0.13 3.74 2.5 3.1	0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88 1.47 2.5	54 ² = 599 24 163 001); ² 139 24 30 30 49 272	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2% 4.7% 4.4% 3.1% 17.3%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45] 0.60 [-0.45, 1.65]	
Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: I.1.6 12h Weline 2011 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: I.1.7 24h Weline 2011 Shatia 2019 Kamal 2018 Okur 2017 Stav 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect:	3.35 2.14 0.75 2.14 0.75 2.0.57; C 2.87 0 3.87 0.5 3.7 2.5 3.7	0.45 $hi^2 = 2$ $\delta (P = 0$ 1.34 0.65 $hi^2 = 2$ 0 0.81 0.49 2.8 $hi^2 = 4$	30 54 .47, df= 0.006) 134 24 158 9.63, df 0.59) 134 24 30 50 268 1.50, df	2.07 = 1 (P = 2.98 0.5 7 = 1 (P 3.24 0.13 3.74 2.5 3.1	0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88 1.47 2.5	54 ² = 599 24 163 001); ² 139 24 30 30 49 272	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2% 4.7% 4.4% 3.1% 17.3%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45] 0.60 [-0.45, 1.65]	
Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: I.1.6 12h Weline 2011 Shatia 2019 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: I.1.7 24h Weline 2011 Shatia 2019 Kamal 2018 Dkur 2017 Stav 2016 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: I.1.8 48h	3.35 2.14 0.75 2.57; C 2.9, 75 0.57; C 2.87 0 3.87 0.5 3.7 0.5 3.7 0.5 2.14 0.75 2.14 0.75 2.14 0.75 2.14 0.75 2.14 0.75 2.14 0.75 2.14 0.75 2.14 0.75 2.14 0.57; C 2.14 0.57; C 0.57; C 0;	0.45 $hi^2 = 2$ $\delta (P = 0$ 1.34 0.65 $hi^2 = 2$ 0 0.81 0.49 2.8 $hi^2 = 4$	30 54 .47, df= 0.006) 134 24 158 9.63, df 0.59) 134 24 30 50 268 1.50, df	2.07 = 1 (P = 2.98 0.5 = 1 (P 3.24 0.13 3.74 2.5 3.1 = 3 (P	0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88 1.47 2.5	54 ² = 599 24 163 001); ² 139 24 30 30 49 272	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2% 4.7% 4.4% 3.1% 17.3%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45] 0.60 [-0.45, 1.65]	
Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: I.1.6 12h Weline 2011 Bhatia 2019 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: I.1.7 24h Weline 2011 Bhatia 2019 Scamal 2018 Soubtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: I.1.8 48h Weline 2011	3.35 2.14 0.75 2.14 0.75 2.0.57; C 2.87 0 3.87 0.5 3.7 2.87 0.5 3.7 2.87 0.5 3.7 2.82 2.87 0.5 2.5 2.87 0.5 2.87 0.5 2.87 0.5 2.87 0.5 2.87 0.5 2.87 0.5 2.87 0.5 2.5 2.87 0.5 2.87 0.5 2.87 0.5 2.87 0.5 2.5 2.87 0.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2	0.45 $hi^{2} = 2$ $\delta (P = 0$ 1.34 0.65 $hi^{2} = 2$ 0 0.82 0 0.81 0.49 2.8 $hi^{2} = 4$ 0 0.49 2.8 $hi^{2} = 4$ 0.49 0.4	30 54 .47, df= 0.006) 134 24 158 9.63, df 0.59) 134 24 30 30 50 268 1.50, df 0.28)	2.07 = 1 (P = 2.98 0.5 (0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88 1.47 2.5 < 0.00	54 P= 599 24 163 001); P 139 24 30 30 49 272 001); P	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2% 4.7% 4.4% 3.1% 17.3% = 93%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45] 0.60 [-0.45, 1.65] -0.46 [-1.29, 0.37]	
Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: 1.1.6 12h Aveline 2011 Bhatia 2019 Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: 1.1.7 24h Aveline 2011 Bhatia 2019 Kamal 2018 Dokur 2017 Stav 2016 Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: 1.1.8 48h Aveline 2011 Dokur 2017	3.35 2.14 0.75 2.14 0.75 2.0.57; C 2.87 0 3.87 0.5 3.7 2.87 0.5 3.7 2.87 0.5 3.7 2.82 2.87 0.5 2.5 2.87 0.5 2.87 0.5 2.87 0.5 2.87 0.5 2.87 0.5 2.87 0.5 2.87 0.5 2.5 2.87 0.5 2.87 0.5 2.87 0.5 2.87 0.5 2.5 2.87 0.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2	0.45 $h ^2 = 2$ $\delta (P = 0$ 1.34 0.65 $h ^2 = 2$ 0 0.82 0 0.81 0.49 2.8 $h ^2 = 4$ $\partial (P = 0$ 1.67	30 54 .47, df= 0.006) 134 24 158 9.63, dt 0.59) 134 24 30 30 50 268 1.50, dt 0.28)	2.07 = 1 (P = 2.98 0.5 (0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88 1.47 2.5 < 0.00 0.73	54 7 = 599 24 163 001); 7 139 24 30 49 272 001); 7 139	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2% 4.7% 3.1% 17.3% = 93% 5.0%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45] 0.60 [-0.45, 1.65] -0.46 [-1.29, 0.37]	
Kamal 2018 Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 1.1.6 12h Aveline 2011 Bhatia 2019 Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 1.1.7 24h Aveline 2011 Bhatia 2019 Kamal 2018 Okur 2017 Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 1.1.8 48h Aveline 2011 Okur 2017 Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect:	3.35 2.14 0.75 2.14 0.75 2.57; C 2.0.57; C 2.87 0 3.87 0.5 3.7 2.63 0.5 2.63 0.5 2.63 0.5	0.45 $hi^2 = 2$ $\delta (P = 0$ 1.34 0.65 $hi^2 = 2$ 0 0.82 0 0.81 0.49 2.8 $hi^2 = 4$ $\delta (P = 0$ 1.67 0.49 0.49 $hi^2 = 0$ 1.67 0.49	30 54 .47, df = 0.006) 134 24 158 9.63, df 0.59) 134 24 30 30 0 50 268 1.50, df 1.28) 134 30 164 .63, df =	2.07 = 1 (P = 2.98 0.5 = 1 (P 3.24 0.13 3.74 2.5 3.1 = 3 (P 2.79 0.5	0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88 1.47 2.5 < 0.00 0.73 0.49	54 P = 599 24 163 001); P 139 24 30 30 29 272 001); P 139 30 169	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2% 4.7% 4.4% 3.1% 17.3% = 93% 5.0% 5.1% 10.0%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45] 0.60 [-0.45, 1.65] -0.46 [-1.29, 0.37] -0.16 [-0.47, 0.15] 0.00 [-0.25, 0.25]	
Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: 1.1.6 12h Aveline 2011 Bhatia 2019 Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: 1.1.7 24h Aveline 2011 Bhatia 2019 Kamal 2018 Okur 2017 Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: 1.1.8 48h Aveline 2011 Okur 2017 Subtotal (95% CI) Heterogeneily: Tau ² =	3.35 2.14 0.75 2.14 0.75 2.57; C 2.0.57; C 2.87 0 3.87 0.5 3.7 2.63 0.5 2.63 0.5 2.63 0.5	0.45 $hi^2 = 2$ $\delta (P = 0$ 1.34 0.65 $hi^2 = 2$ 0 0.82 0 0.81 0.49 2.8 $hi^2 = 4$ $\delta (P = 0$ 1.67 0.49 0.49 $hi^2 = 0$ 1.67 0.49	30 54 .47, df = 0.006) 134 24 158 9.63, df 0.59) 134 24 30 30 0 50 268 1.50, df 1.28) 134 30 164 .63, df =	2.07 = 1 (P = 2.98 0.5 = 1 (P 3.24 0.13 3.74 2.5 3.1 = 3 (P 2.79 0.5	0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88 1.47 2.5 < 0.00 0.73 0.49	54 ² = 599 139 24 163 001); ² 139 24 30 49 272 001); ² 139 30 169 ² = 0%	5.0% 8.3% 5.0% 5.0% 10.0% = 97% 5.2% 4.7% 4.4% 3.1% 17.3% = 93% 5.0% 5.1% 10.0%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45] 0.60 [-0.45, 1.65] -0.46 [-1.29, 0.37] -0.16 [-0.47, 0.15] 0.00 [-0.25, 0.25]	
Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: 1.1.6 12h Aveline 2011 Bhatia 2019 Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: 1.1.7 24h Aveline 2011 Bhatia 2019 Kamal 2018 Okur 2017 Stav 2016 Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: 1.1.8 48h Aveline 2011 Okur 2017 Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect: Total (95% CI)	3.35 2.14 0.75 2.14 0.75 0.57; C 2.87 0 3.87 0.5 3.7 0.5 3.7 2.63 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	0.45 $h ^2 = 2$ $\delta (P = 0$ 1.34 0.65 $h ^2 = 2$ 4 (P = 0 0.82 0.82 0.82 0.82 0.84 0.49 2.8 $h ^2 = 4$ 0.49 1.67 0.49 $h ^2 = 0$ 1.67 0.49 $h ^2 = 0$	30 54 .47, df = 0.006) 134 24 158 9.63, df 0.59) 134 24 30 50 268 1.50, df 0.28) 134 30 164 .63, df = 0.52) 1090	2.07 = 1 (P = 2.98 0.5 '= 1 (P 3.24 0.13 3.74 2.5 3.1 2.79 0.5 = 3 (P 2.79 0.5 = 1 (P =	0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88 1.47 2.5 < 0.00 0.73 0.49 0.43);	54 ² = 599 139 24 163 001); ² 139 24 30 49 272 001); ² 139 30 169 ² = 0% 1109	5.0% 8.3% 5.0% 5.0% 10.0% 97% 5.2% 4.7% 4.4% 3.1% 17.3% = 93% 5.0% 5.1% 10.0%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45] 0.60 [-0.45, 1.65] -0.46 [-1.29, 0.37] -0.16 [-0.47, 0.15] 0.00 [-0.25, 0.25] -0.06 [-0.26, 0.13] 0.10 [-0.18, 0.38]	
Subtotal (95% Cl) Heterogeneily: Tau ² = Test for overall effect: 1.1.6 12h Aveline 2011 Bhatia 2019 Subtotal (95% Cl) Heterogeneily: Tau ² = Test for overall effect: 1.1.7 24h Aveline 2011 Bhatia 2019 Kamal 2018 Okur 2017 Stav 2016 Subtotal (95% Cl) Heterogeneily: Tau ² = Test for overall effect: 1.1.8 48h Aveline 2011 Okur 2017 Subtotal (95% Cl) Heterogeneily: Tau ² = Test for overall effect:	3.35 2.14 0.75 2.14 0.75 2.57; C 2.87 0 3.87 0.5 3.7 2.63 0.5 0.5 2.63 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	0.45 $h ^2 = 2$ $\delta (P = 0$ 1.34 0.65 $h ^2 = 2$ 0 0.82 0 0.81 0.49 2.8 $h ^2 = 4$ $\delta (P = 0$ 1.67 0.49 $h ^2 = 0$ $h ^2 = 0$ $h ^2 = 0$ $h ^2 = 1$ $h ^2 = $	30 54 .47, df = 0.006) 134 24 158 9.63, df 0.59) 134 24 30 30 0 50 268 1.50, df 1.28) 134 30 164 .63, df = 0.52) 1090	2.07 = 1 (P = 2.98 0.5 '= 1 (P 3.24 0.13 3.74 2.5 3.1 2.79 0.5 = 3 (P 2.79 0.5 = 1 (P =	0.12); 0.95 0.25 < 0.00 0.62 0.13 0.88 1.47 2.5 < 0.00 0.73 0.49 0.43);	54 ² = 599 139 24 163 001); ² 139 24 30 49 272 001); ² 139 30 169 ² = 0% 1109	5.0% 8.3% 5.0% 5.0% 10.0% 97% 5.2% 4.7% 4.4% 3.1% 17.3% = 93% 5.0% 5.1% 10.0%	1.28 [0.98, 1.58] 1.02 [0.30, 1.74] -0.84 [-1.12, -0.56] 0.25 [-0.03, 0.53] -0.30 [-1.36, 0.77] -0.37 [-0.54, -0.20] Not estimable 0.13 [-0.30, 0.56] -2.00 [-2.55, -1.45] 0.60 [-0.45, 1.65] -0.46 [-1.29, 0.37] -0.16 [-0.47, 0.15] 0.00 [-0.25, 0.25] -0.06 [-0.26, 0.13] 0.10 [-0.18, 0.38]	-4 -2 0 2 4 wours [experimental] Favours [control]

3.10. Patient satisfaction with the quality of analgesia Three studies $^{[9,13,18]}$ comparing TAP (100 patients) with II/IH (100 patients) showed no significant difference in patient satisfaction with the quality of analgesia between the II/IH group and the TAP group (RR=0.69; 95% CI 0.37-1.31, $l^2 = 77\%$; P = .26) (Fig. 9). No sensitivity analysis was conducted due to none of the included studies were eligible for exclusion.

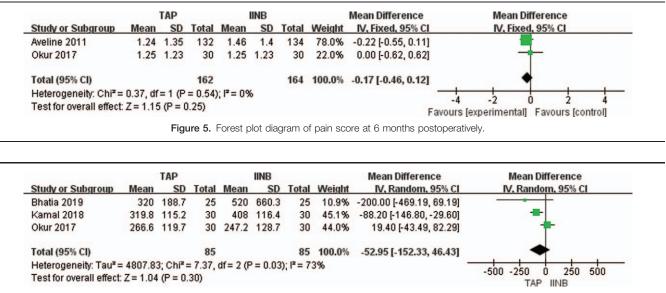


Figure 6. Forest plot diagram of the time to first request for rescue analgesic.

3.11. Quality of evidence

The GRADE system was used to evaluate the quality of outcomes in the current study. The overall evidence for each outcome was low to very low, which may lower the confidence in any recommendations. The detail of each assessment is listed in Table 2.

4. Discussion

Both TAP and II/IH have been previously demonstrated as effective components of multimodal analgesia to reduce postoperative pain following hernia repair. However, it is still uncertain that which of the 2 methods is better. Our metaanalysis demonstrates that there are no significant differences between the 2 methods regarding the intravenous equivalent morphine consumption 24 hours postoperatively, PONV 24 hours postoperatively, the time to first request for rescue analgesic, the incidence of complication related with the nerve block, and the patients' satisfaction. Moreover, our meta-analysis suggests that the patients who underwent II/IH block are showed to have lower pain scores at 6 and 8 hours postoperatively than patients who underwent TAP block. However, the pain scores at 1, 2, 4, 12, 24, 48 hours postoperatively and the pain intensity 6 months after the surgery are comparable between the TAP group and II/IH group.

Anatomically, sensory innervation of the inguinal region is greatly supplied by the T12-L2 nerves.^[12] The ilioinguinal and iliohypogastric nerves, which are branches of T12 and L1, pass between the internal oblique and transversus abdominis muscles at the level immediately superior to the anterior superior iliac spine.^[12] Local anesthetic is deposited in the plane between the internal oblique and transverse abdominis muscle in both TAP and II/IH block, but at different points along the course of the nerves, with the local anesthetic being administered closer to the nerve in II/IH block. Therefore, II/IH block may require fewer local anesthetic than TAP block to achieve similar analgesic effect, especially when II/IH block is performed under ultrasound guidance.^[19] In the current meta-analysis, we found that pain scores were significantly lower in group II/IH than in group TAP at 6 and 8 hours, while no difference was found at other time points. As showed in Table 1, both II/IH block and TAP block were performed under ultrasound guidance in the studies

	TAP		IINB			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Aveline 2011	12	134	15	139	80.8%	0.83 [0.40, 1.71]	
Bhatia 2019	0	25	0	25		Not estimable	
Faiz 2019	3	45	1	45	5.5%	3.00 [0.32, 27.76]	
Kamal 2018	2	30	0	30	2.7%	5.00 [0.25, 99.95]	
Okur 2017	0	30	1	30	8.2%	0.33 [0.01, 7.87]	3
Stav 2016	1	50	0	49	2.8%	2.94 [0.12, 70.50]	
Total (95% CI)		314		318	100.0%	1.08 [0.59, 1.99]	★
Total events	18		17				
Heterogeneity: Chi ² =	3.24, df=	4 (P =	0.52); I ² =	= 0%			
Test for overall effect	Z= 0.25	(P = 0.8	30)			6	0.01 0.1 1 10 100 Favours [experimental] Favours [control]

Figure 7. Forest plot diagram of the incidence of PONV at 24 hours postoperatively. PONV = postoperative nausea and vomiting.

s Total 0 134 0 25	Events 1	Total 139		M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% Cl	
5 . T	1	120						
0 25		139	18.5%	0.35 [0.01, 8.41]	-			
- 20	0	25		Not estimable				
0 30	2	30	31.4%	0.20 [0.01, 4.00]		-	<u> </u>	
7 30	4	30	50.2%	1.75 [0.57, 5.36]				
0 50	0	49		Not estimable				
269		273	100.0%	1.00 [0.40, 2.52]				
7	7							
f= 2 (P =	0.29); I ² =	20%				1	1	
					0.01			100
	7 30 0 50 269 7 #f= 2 (P =	7 30 4 0 50 0 269 7 7	7 30 4 30 0 50 0 49 269 273 7 7 If = 2 (P = 0.29); ² = 20%	7 30 4 30 50.2% 0 50 0 49 269 273 100.0% 7 7 if = 2 (P = 0.29); I [≈] = 20%	7 30 4 30 50.2% 1.75 [0.57, 5.36] 0 50 0 49 Not estimable 269 273 100.0% 1.00 [0.40, 2.52] 7 7 7 if = 2 (P = 0.29); I ² = 20% 100	7 30 4 30 50.2% 1.75 [0.57, 5.36] 0 50 0 49 Not estimable 269 273 100.0% 1.00 [0.40, 2.52] 7 7 7 100.0% 1.00 [0.40, 2.52] 16 - 20%	7 30 4 30 50.2% 1.75 [0.57, 5.36] - 0 50 0 49 Not estimable 269 273 100.0% 1.00 [0.40, 2.52] - 7 7 7 - if = 2 (P = 0.29); ² = 20% - - -	7 30 4 30 50.2% 1.75 [0.57, 5.36] 0 50 0 49 Not estimable 269 273 100.0% 1.00 [0.40, 2.52] 7 7 7 aff = 2 (P = 0.29); $P = 20\%$ 0.01 0.1 11 (P = 0.99) 0.01 0.1 10

	TAP	,	IINE			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bhatia 2019	14	24	11	24	33.3%	1.27 [0.73, 2.21]	
Kamal 2018	20	30	28	30	41.0%	0.71 [0.54, 0.94]	-
Faiz 2019	6	45	20	45	25.7%	0.30 [0.13, 0.68]	
Total (95% CI)		99		99	100.0%	0.69 [0.37, 1.31]	•
Total events	40		59				
Heterogeneity: Tau ² =	= 0.24; Ch	i ² = 9.0	2, df = 2 (P = 0.0	1); I ² = 78	1%	
Test for overall effect	Z=1.13	(P = 0.2)	26)				0.01 0.1 1 10 100 TAP IINB

Figure 9. Forest plot diagram of the patient satisfaction with the quality of analgesia.

Table 2

Quality of the evidence.

Outcomes	No. of participants (studies) follow-up	Quality of the evidence (GRADE)	Anticipated absolute effects
Total opioid consumption at 24 hours	512 (4 studies)	Low	MD 0.03 higher
	24 hours	Due to risk of bias, inconsistency	(1.23 lower to 1.28 higher)
Pain score at 1 hour	168 (3 studies)	Low	MD 0.03 lower
	1 hour	Due to risk of bias, imprecision	(0.24 lower, 0.17 higher)
Pain score at 2 hours	168 (3 studies)	Very low	MD 0.32 higher
	2 hours	Due to risk of bias, imprecision, inconsistency	(0.47 lower to 1.1 higher)
Pain score at 4 hours	441 (4 studies)	Low	MD 0.11 higher
	4 hours	Due to risk of bias, inconsistency	(0.84 lower to 1.07 higher)
Pain score at 6 hours	120 (2 studies)	Low	MD 0.94 higher
	6 hours	Due to risk of bias, imprecision	(0.67-1.22 higher)
Pain score at 8 hours	108 (2 studies)	Low	MD 1.02 higher
	8 hours	Due to inconsistency, imprecision	(0.30–1.74 higher)
Pain score at 12 hours	321 (2 studies)	Low	MD 0.30 lower
	12 hours	Due to inconsistency, imprecision	(1.36 lower to 0.77 higher)
Pain score at 24 hours	540 (5 studies)	Low	MD 0.46 lower
	24 hours	Due to risk of bias, inconsistency	(1.29 lower to 0.37 higher)
Pain score at 48 hours	333 (2 studies)	Low	MD 0.06 lower
	48 hours	Due to risk of bias, imprecision	(0.26 lower to 0.13 higher)
Pain score at 6 months	326 (2 studies)	Low	MD 0.17 lower
	6 months	Due to risk of bias, imprecision	(0.46 lower to 0.12 higher)
Time to first request for rescue analgesic	170 (3 studies)	Very low	MD 52.95 lower
		Due to risk of bias, imprecision, inconsistency	(152.33 lower to 46.43 higher)
Incidence of PONV at 24 hours	582 (5 studies)	Moderate	RR 1.08 higher
	24 hours	Due to risk of bias	(0.59–1.99 higher)
Incidence of complication related with nerve block	393 (3 studies)	Low	RR 1.00 higher
		Due to risk of bias, imprecision	(0.40-2.52 higher)
Patient satisfaction with the quality of analgesia	198 (3 studies)	Very low	RR 0.69 higher
		Due to risk of bias, imprecision, inconsistency	(0.37-1.31 higher)

GRADE=Grading of Recommendations Assessment, MD=mean difference, PONV=postoperative nausea and vomiting, RR=risk ratio.

included in the meta-analysis and the dose of local anesthetic were also comparable in both groups. Therefore, II/IH may provide higher drug concentration around the target nerves, and as the quantity of the local anesthetic decreases over time, the advantages of II/IH block gradually become prominent. The inadequate blockade of the genital branch of the genitofemoral nerve could also partly explain the difference in analgesia between groups. Local anesthetic may spread to the deep ring and block the genital branch of the genitofemoral nerve in II/IH block, while this medial spread would be less likely to occur in TAP block. In addition, the well documented pain relief with ilioinguinal nerve block and wound infiltration is reported to have a limited duration of action of up to 6 to 8 hours.^[20] The above reasons may explain our findings in postoperative pain scores at different time points. Moreover, we need to be cautious about the above results due to the significant heterogeneity and small sample size in our meta-analysis. Further studies with larger number of population size are needed to determine the analgesic effect between the II/IH and TAP block.

Multiple causes and mechanism may account for chronic pain after inguinal hernia repair.^[21] Poor postoperative analgesia and intraoperative nerve damage may be the main causes of chronic pain.^[22] Our results did not document any significant difference in the occurrence of chronic pain after hernia repair with TAP block when compared with IHN block which is probably due to the similar overall postoperative pain scores between the 2 groups.

Our current studied did not suggest any difference in intravenous equivalent morphine consumption at 24 hours postoperatively, time to the first request for rescue analgesia and patients satisfaction. The similar overall postoperative pain scores between the 2 groups may be a potential explanation for this phenomenon. However, differences in postoperative analgesia regimen among the included studies should be taken into consideration when we deal with these results.

There are a limited number of reported complications for TAP block and II/IH block. Intraperitoneal injection and liver laceration have been reported in TAP block,^[23] and colon perforation and pelvic hematoma are reported to occur following II/IH block.^[24,25] The anatomic landmark technique in performing the block may account for these complications. Our current study showed no significant difference in complication associated with nerve block between the TAP group and II/IH block probably due to the widespread use of ultrasound in performing nerve block in most included studies. Moreover, no significant difference in PONV was found in the current study which may be explained by the similar intravenous equivalent morphine consumption at 24 hours postoperatively.

Although we have tried our best to reduce the heterogeneity by adopting rigorous inclusion and exclusion criteria, there were still factors that may influence the power to interrogate the efficacy of TAP block and II/IH in inguinal hernia repair. Different types of opioid were used in the studies included in our meta-analysis. Although equivalent dose conversions were carried out as other studies did,^[26] variation may exist in the process of dose conversions.^[27] In addition, supplementary analgesics such as paracetamol and other nonsteroidal anti-inflammatory drugs are adopted in some trials, which make it more difficult to compare the opioid consumption among trials. Despite the above factors that contribute to the heterogeneity of the analysis, there are some other limitations in the current study. Firstly, we did not include a study which was conducted in children.^[12] Secondly, we did not test for publication bias for our outcomes, as only 6 studies were included, and tests of publication bias are not recommended if <10 studies are included.^[28] Finally, we failed to acquire additional data of some included studies, although we have tried our best to contact the corresponding authors. Despite the above limitations, our study is still the most comprehensive review on this topic and more studies should be conducted regarding on the optimal dose of local anesthetic and the block sites in TAP and II/ IH block for postoperative analgesia following inguinal hernia repair.

In conclusion, this meta-analysis found no significant differences in postoperative opioid use, the time to first request for rescue analgesia, the incidence of postoperative nausea and vomiting (PONV), the incidence of complication associated with the nerve block and patient satisfaction after inguinal hernia repair between TAP block and II/IH block. However, patients who underwent II/IH block are showed to have lower pain scores at 6 and 8 hours postoperatively than those who underwent TAP block. However, the pain scores at 1, 2, 4, 12, 24, 48 hours postoperatively are comparable between groups. Therefore, II/IH block may be more recommended when the same type and dose of local anesthetic are adopted when compared with TAP block. However, more high-quality RCTs with long-term follow-up are still required to make the conclusion.

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