

SUPPLEMENTARY TABLES

Supplementary Table 1. Cochrane Risk of Bias Assessment

Analgesic	Author	Year	Random sequence generation	Allocation concealment	Blinding (participants and personnel)	Incomplete outcome data addressed?	Free of selecting reporting	Free of other bias	Overall risk of bias
NSAID	Karamanlioglu et al	2005	Low	Low	Low	Unclear	Unclear	Low	Unclear
	Arslan et al	2006	Low	Low	Low	Unclear	Unclear	Unclear	Unclear
	Yücel et al	2016	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear
	Kim et al	2008	Low	Unclear	Unclear	Unclear	Unclear	High	High
	Schopf et al	2012	Low	Unclear	Unclear	High	Unclear	Unclear	High
	Smirnov et al	2008	Low	Low	Low	Low	Low	Low	Low
Acetaminophen	Hong et al	2010	Low	Low	Unclear	Low	Unclear	Unclear	Unclear
	Lee et al	2010	High	High	Unclear	Unclear	High	Unclear	High
	Abdelmageed et al	2014	Low	Unclear	Low	Unclear	Unclear	Low	Unclear
Gabapentinoids	Kim et al	2010	Low	Low	Low	Unclear	Unclear	Low	Low
	Brogly et al	2008	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
	Hema et al	2017	NA	NA	NA	NA	NA	NA	NA
	Bindu et al	2015	NA	NA	NA	NA	NA	NA	NA
Local Anesthetics	Egan et al	2013	Low	Low	Low	Unclear	Unclear	Unclear	Unclear
	Teksoz et al	2016	Low	Low	Low	Low	Unclear	Low	Low
	Dumlu et al	2016	Unclear	Unclear	High	Low	Unclear	Unclear	High
	Choi et al	2016	Low	Low	Low	Low	Unclear	Low	Low
	Santosh et al	2016	Low	Low	Low	Unclear	Unclear	Unclear	Unclear
	Miu et al	2016	Low	Low	Low	Unclear	Unclear	High	Unclear
	Kang et al	2015	Low	Low	Low	Unclear	Unclear	Unclear	High
	Gürkan et al	2015	Low	Low	Unclear	Low	Unclear	Low	Unclear

	Sellami et al	2018	Low	Low	Low	Low	Low	Unclear	Low
	Karthikeyan et al	2013	Low	Low	Low	Unclear	Unclear	Unclear	Unclear
	Lacoste et al	1997	Low	Unclear	Low	Unclear	Unclear	Low	Unclear
	Eti et al	2006	Low	Low	Low	Unclear	Unclear	NA	Low
	Black et al	2007	NA	NA	NA	NA	NA	Low	NA
	Kesisoglou et al	2010	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
	Shin et al	2012	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear
	Ekinci et al	2017	Unclear	High	High	Unclear	Unclear	Unclear	High
	Andrieu et al	2007	Low	Low	Low	Unclear	Unclear	Unclear	Low
	Herbland et al	2006	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear
	Ryu et al	2015	Low	Low	Low	Low	Unclear	Low	Low
	Ahiskalioglu et al	2018	Low	Low	Low	Unclear	Unclear	Low	Low
	Choi et al	2017	Low	Low	Low	Low	Unclear	Unclear	Low
Ketamine	Kim et al	2016	Low	Unclear	Low	Low	High	Unclear	High
	Abd El-Rahman et al	2018	Low	Low	Low	Unclear	Unclear	Unclear	Unclear
	Lee et al	2018	Low	Unclear	Unclear	Low	Unclear	Low	Unclear
Other	Kim et al	2017	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear

NA = Not Applicable

Supplementary Table 2. Analgesic used for Thyroidectomy/Parathyroidectomy: NSAID

Author	Year	Preparation Investigated (Dose)	Time Given	Rescue Med (Dose) + Timing	Total Rescue Analgesic Consumption	Time to first rescue
Karamanlioglu et al	2005	1. S-Saline 2. R-Ropivacaine (0.75%) 3. L- Lornoxicam (8 mg) 4. RL- Ropivacaine (0.75%) with Lornoxicam (8 mg)	Prior to skin closure	Pethidine (1mg/kg); for VAS >4	NR	1. 5.9 ± 5.2 hr 2. 10.7 ± 8.3 hr 3. 11.1 ± 7.7 hr
Arslan et al	2006	1. L- IV (8mg) Lornoxicam + IV (8mg) lornoxicam for 24 hrs postop 2. P- Saline + saline infusion 24 hrs postop	End of operation	NR	100±45.5mg (L) 250±104.6mg (P)	1. 101.7±72.3 min 2. 37.9±15.1 min
Yücel et al	2016	1. IV Lornoxicam (8mg) 2. IV Tramadol (1 mg/kg)	Postoperatively	Diclofenac (75mg); for VAS >4		1. 98.36±45.21 min 2. 74.86±34.58 min
Kim et al	2008	1. Fentanyl (15 µg/kg) 2. Fentanyl (12.5 µg/kg) and ketorolac (1.5 mg/kg) 3. Fentanyl (10 µg/kg) and ketorolac (3 mg/kg)	Preoperatively	Fentanyl (50microg)	NR	NR
Schopf et al	2012	1. Etoricoxib (120mg) + 10ml ropivacaine (10mg/ml) 2. Etoricoxib (120mg) + 10 mL saline 3. Placebo + ropivacaine (10mg/ml) 4. Placebo + saline		NR	NR	NR
Smirnov et al	2008	1. Etoricoxib (120 mg) 2. Placebo	1 hour prior to surgery	Oxycodone (2 mg); VAS >3 at rest	1. 8.9 ± 5.3mg 2. 7.8 ± 3.8mg	1. 43 ± 49 min 2. 42 ± 29 min

hr = hour; IV = intravenous; min = minute; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; VAS = visual analog scale.

Supplementary Table 3. Analgesic used for Thyroidectomy/Parathyroidectomy: Acetaminophen

Author	Year	Preparation Investigated (Dose)	Time Given	Rescue Med (Dose) + Timing	Total Rescue Analgesic Consumption	Time to first rescue (min)
Hong et al	2010	1. Paracetamol (1g) 2. Placebo	1 hour prior to induction	Fentanyl (0.1 µg/kg) for VAS >7; ketorolac (1 mg/kg) for 6 ≥ VAS ≥ 4	NR	1. 113.5 min 2. 53.5 min
Lee et al	2010	1. Normal saline 2. Ketorolac (30 mg) 3. Paracetamol (1 g) 4. Paracetamol (700 mg) plus morphine (3 mg)	Pethidine hydrochloride (25 mg)	NR	NR	NR
Abdelmageed et al	2014	1. Paracetamol (1g) 2. Saline	Just before anesthesia induction	Meperidine 20mg; for VAS >3	1. 23.1 ± 9.0mg 2. 28.7 ± 10.2mg	1. 48.4 ± 14.0 min 2. 40.7 ± 11.5 min

Min = minute; NR = not reported; VAS = visual analog scale

Supplementary Table 4. Analgesic used for Thyroidectomy/Parathyroidectomy: Gabapentinoids

Author	Year	Preparation Investigated (Dose)	Time Given	Rescue Med (Dose) + Timing	Total Rescue Analgesic Consumption	Time to first rescue
Kim et al	2010	1. Pregabalin (150 mg) 2. Placebo	1 hour before surgery and 12 hours after initial dose	Fentanyl (50 µg); for VAS >5	NR	NR
Brogly et al	2008	1. Gabapentin (1200 mg) 2. Placebo	2 hours prior to surgery	IV Tramadol (50mg)	NR	NR
Hema et al	2017	1. Oral gabapentin (600 mg) 2. Diazepam (10 mg)	2 hours prior to surgery	Tramadol (50mg)	1. 63.45 ± 34.7mg 2. 111.83 ± 24.65mg	NR
Bindu et al	2015	1. Oral pregabalin (300 mg) 2. No preoperative pregabalin	1 hour prior to surgery	Morphine (0.1 mg/kg); for VAS >4	NR	1. 322.07 ± 69.106 min 2. 256.33 ± 111.978 min

Min = minute; NR = not reported; NS = normal saline; VAS = visual analog scale.

Supplementary Table 5. Analgesic used for Thyroidectomy/Parathyroidectomy: Local Anesthetics

Author	Year	Preparation Investigated (Dose)	Time Given	Rescue Med (Dose) + Timing	Total Rescue Analgesic Consumption	Time to first rescue
Egan et al	2013	1. Bupivacaine (0.5%) with 1:200000 adrenaline 2. Bupivacaine (0.5%) with 1:200000 adrenaline plus intraoperative SCPB plus an additional 5 ml Bupivacaine (0.5%) with 1:200000 adrenaline	1. Before incision 2. Before incision + intraoperative	Tramadol	NR	NR
Teksoz et al	2016	1. 10-mL of bupivacaine solution (0.5%) 2. NaCl (0.9%)	At the end of surgery	Paracetamol IV (1 gram)	NR	NR
Dumlu et al	2016	1. No intervention 2. Paratracheal bupivacaine (0.25%) 3. Subcutaneous bupivacaine (0.25%)	Following thyroidectomy	Diclofenac (75 mg/amp); for VAS >5	NR	NR
Choi et al	2016	1. Lidocaine (1.5 mg/kg) preop with (2 mg/kg/h) infusion during surgery 2. Same volume of normal saline	Prior to anesthesia	Fentanyl (50 µg); VAS>30 (100-point scale)	1. 550.79 ± 46.46 µg 2. 598.57 ± 55.58 µg	NR
Santosh et al	2016	1. Ropivacaine (20 ml 0.5%) 2. Ropivacaine (20 ml 0.5%) with 0.5 µg/kg dexmedetomidine after induction of anesthesia	Prior to anesthesia	Tramadol (50 mg); for VAS >3	1. 110.27 ± 20.12 µg 2. 0	NR
Miu et al	2016	1. Sodium chloride solution (0.9%) 2. Ropivacaine (10 mL of 0.75%)	Prior to skin closure	IV Morphine titration; for VAS > 30 (100-point scale)	NR	NR
Kang et al	2015	1. Saline solution (0.9% 3 mL/kg) 2. Ropivacaine with saline (0.1% 3 mg/kg)	Prior to anesthesia	Fentanyl (50 µg); for VAS>40 (100-point scale)	1. 510.75 µg 2. 422.50 µg	NR
Gürkan et al	2015	1. Bupivacaine (0.25%) 2. No BSCP intervention	20 mins prior to induction	Morphine	NR	NR
Sellami et al	2018	1. Saline 2. Bupivacaine (0.5%)	After skin closures	Nefopam (20mg); for VAS >40 (100-point scale)	NR	NR
Karthikeyan et al	2013	1. Bupivacaine (15 mL 0.25%) 2. Bupivacaine (0.25%) with (1 µg/kg) clonidine 3. Normal Saline (0.9%)	After induction	Morphine (1mg) PCA	1. 30.70 ± 4.77mg 2. 26.45 ± 3.41mg 3. 40.85 ± 3.95 mg	1. 113 min 2. 80 min 3. 35 min
Lacoste et al	1997	1. Oral controlled-release morphine 2. Sublingual buprenorphine (0.2 mg) 3. Bupivacaine solution (0.25%)	Before skin closure	NR	NR	NR
Eti et al	2006	1. BSCP Bupivacaine (0.25%) 2. Local anesthetic wound infiltration with bupivacaine (20 mL 0.25%) 3. No regional block control	Following intubation	Meperidine (10 mg/mL); for VAS>3	1. 440.1 ± 210.2mg 2. 400.0 ± 160.8mg 3. 370.2 ± 250.8mg	1. 29.6 ± 17.8min 2. 25.7 ± 11.5min 3. 13.5 ± 6.3min
Black et al	2007	1. Lidocaine (1%) local cervical block 2. Desflurane general anesthesia	At induction	morphine equivalents	1. 11.4 ± 1.3 mg 2. 22.5 ± 1.1 mg	NR
Kesisoglou et al	2010	1. Saline 2. Ropivacaine (0.75%)	At the end of surgery	Dextropropoxyphene hydrochloride (75mg)	NR	NR
Shin et al	2012	1. BSCP Bupivacaine (20 mL of 0.525%) 2. Isotonic sodium chloride solution 3. Local wound infiltration Ropivacaine (20 mL of 0.525%)	At the end of surgery	Ketorolac (60mg); for VAS>40 (100-point scale)	NR	NR
Ekinci et al	2017	1. Wound infiltration with levobupivacaine (0.25%) 2. Wound infiltration with (0.25%) levobupivacaine	1. Before incision 2. After incision	Tramadol (0.5mg/kg); for VAS>4	1. 72.4 ± 24.5mg 2. 91.5 ± 36.8 mg	1. 159.4 ± 78.6 min 2. 118.6 ± 56.4 min

Andrieu et al	2007	1. P- BSCPb with saline 2. R- Ropivacaine (0.487%) 3. RC- Ropivacaine (0.487%) plus clonidine (5 µg/ml)	At the end of surgery	Nefopam (20mg); for VAS >4	NR	NR
Herbland et al	2006	1. Control - no block 2. Preop BSCPb Ropivacaine (0.75%) 3. Postop BSCPb Ropivacaine (0.75%)	At the end of surgery	NR	NR	NR
Ryu et al	2015	1. Levobupivacaine spray (30 ml of 0.25 %) 2. Normal saline spray (30ml)	At the end of surgery	Fentanyl (12µg/ml)	NR	NR
Ahiskalioglu et al	2018	1. BSCPb with 0.9% saline + oral placebo 2. BSCPb with bupivacaine (0.25%) + oral placebo 3. BSCPb with bupivacaine (0.25%) + tizanidine (6 mg) capsule	45 min prior to surgery	Meperidine (25mg); for VAS>4	1. 86.25 ± 42.52mg	NR
Choi et al	2017	1. Lidocaine (2 mg/kg) + (3 mg/kg/h) IV lidocaine 2. Normal saline (0.9%)	During anesthesia	Fentanyl (50 µg) in the PACU or Tramadol (25 mg) on the ward; for VAS>4	Fentanyl: 1. 31.4 ± 37.8µg; 2. 41.5 ± 41.7µg Tramadol: 1. 72.0 ± 53.7mg; 2. 73.3 ± 54.9	NR

BSCPb = bilateral superficial cervical plexus block; IV = intravenous; NR = not reported; NS = normal saline; PACU = post-anesthesia care unit; PCA = patient controlled analgesia; VAS = visual analog scale.

Supplementary Table 6. Ketamine - Summary of Evidence and Conclusions

Authors	Study Year	LOE (1a-5)	Jadad Score	Study Design	Randomization	Surgery Type	Male:Female	Age (Mean)	Study Groups (n)	Clinical Endpoint	Conclusions
Kim et al	2016	1b	5	Prospective double-blinded RCT	Computer-generated	Thyroid	1. 0:28 2. 2:27	1. 40 ± 9 2. 39 ± 8	Control: 1. 1 mg/kg bolus, 60 µg/kg/h continuous infusion of saline (28) Intervention: 2. 1 mg/kg bolus, 60 µg/kg/h continuous infusion of ketamine (29)	NRS pain scores, consumption of rescue analgesics, and postoperative adverse effects were assessed at 1, 6, 24, and 48 hours postoperatively.	Intravenous ketamine infusion during anesthesia resulted in lower postoperative pain scores following BABA robotic or endoscopic thyroidectomy, with no increase in adverse events.
Abd El-Rahman et al	2018	1b	3	Prospective double-blinded RCT	Computer-generated	Thyroid	1. 6:24 2. 9:21 3. 8:22	1. 44.7 ± 10.9 2. 44.6 ± 12.2 3. 40.9 ± 13.2	Control: 1. 10 mL of normal saline instilled in the wound (30) Intervention: 2. 1 mg/kg ketamine in a total volume of 10 mL normal saline instilled in the wound (30) 3. 1 mg/kg of intramuscular ketamine (30)	VAS pain scores 1, 2, 4, 6, 12, and 24 hours postoperatively; total morphine consumption, time to first analgesia, adverse effects	Local wound ketamine instillation provided superior postoperative analgesia with lower incidence of side effects in comparison with IM ketamine and placebo following total thyroidectomy.
Lee et al	2018	1b	3	Prospective single blinded RCT	Computer-generated	Thyroid	1. 4:28 2. 2:30	1. 37 ± 12 2. 38 ± 9	Control: 1. Continuous infusion of saline at 2 µg/kg/min (32) Intervention: 2. 0.15-mg/kg bolus ketamine with continuous infusion at 2 µg/kg/min (32)	VAS pain scores at 0, 1, 24, and 48 h postoperatively; time to first analgesic request, total analgesic demand, adverse effects	Ketamine infusion decreased pain scores for 24 h postoperatively and reduced analgesic requirements without serious complications in patients following thyroidectomy.

BABA = bilateral axillo-breast approach; IM = intramuscular; LOE = level of evidence; RCT = randomized, controlled trial; VAS = visual analog scale.

Supplementary Table 7. Acetaminophen - Summary of Evidence and Conclusions

Authors	Study Year	LOE (1a-5)	Jadad Score	Study Design	Randomization	Surgery Type	Male:Female	Age (Mean, yrs)	Study Groups (n)	Clinical Endpoint	Conclusions
Hong et al	2010	1b	4	Prospective double-blind RCT	Randomization Tables	Thyroid	1. 0:61 2. 0:63	1. 42.7 ± 9.4 2. 40.0 ± 9.1	Control: 1. Placebo (61) Intervention: 2. Paracetamol as a 100-ml solution infused over 15 min 1 h before the induction of anesthesia, and then at 6-h intervals for the following 24 h (63)	Postoperative VAS, analgesic consumption, time to first analgesic, adverse events	Repeated administration of 1 g of intravenous paracetamol over 24 h is easy, effective, safe, and well tolerated for pain management in patients with moderate to severe postoperative pain after gasless robot-assisted endoscopic thyroidectomy performed via the transaxillary approach.
Lee et al	2010	1b	2	Prospective double-blind RCT	Not specified	Thyroid	1. 0:20 2. 0:20 3. 0:20 4. 0:20	1. 46.3 ± 9.5 2. 46.1 ± 9.9 3. 44.7 ± 7.3 4. 45.2 ± 9.4	Control: 1. Normal saline (20) Interventions: 2. Ketorolac (20) 3. Paracetamol (20) 4. Paracetamol + morphine (20)	Pain intensity using a visual analogue scale (VAS) at 0.5, 1, 2, 4, and 6 hrs after the end of surgery; adverse events Sevoflurane consumption during thyroidectomy;	Paracetamol 1 g IV possesses a similar analgesic efficacy to ketorolac 30 mg IV after thyroidectomy. Paracetamol may represent an alternative to ketorolac for pain prevention after mildly to moderately painful surgery in situations where the use of NSAIDs is unsuitable.
Abdelmageed et al	2014	1b	4	Prospective double-blinded RCT	Computer-generated	Thyroid	1. 2:29 2. 3:28	1. 31.9 ± 3.1 2. 32.2 ± 3.4	Control: 1. Saline (31) Intervention: 2. Paracetamol (31)	postoperative VAS and sedation scores at 0, 2, 4, 6 hours; postoperative meperidine consumption; adverse events	Preoperative paracetamol administration reduces sevoflurane consumption during thyroidectomy and postoperative meperidine consumption.

AE = adverse effects; IV = intravenous; LOE = level of evidence; NRS = numeric rating scale; NS = normal saline; NSAID = nonsteroidal anti-inflammatory drug; PACU = post-anesthesia care unit; RCT = randomized, controlled trial; VAS = visual analog scale.