Clinical Guidance for Acute Postoperative Pain Management 2019 The Royal College of Anesthesiologists of Thailand (RCAT) and The Thai Association for the Study of Pain (TASP) : Second Edition

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There have been significant new developments in the field of acute postoperative pain management in the past decade. Improvement of acute postoperative pain management is an ongoing process. Recently, the Royal College of Anesthesiologists of Thailand (RCAT), in collaboration with the Thai Association for the Study of Pain (TASP), released a second edition of Clinical Guidance for acute postoperative pain management (2019), focusing on individualized patient assessment and treatment during perioperative period with the concepts of multimodal analgesia, preventive analgesia and surgery-specific pain management. The primary goals of acute postoperative pain management are efficient pain control to hasten the patient's recovery, shorten hospital stay, minimize adverse effects, improve the patient's functional outcome and satisfaction as well as prevent chronic pain after surgery. Clinicians' ability to select individualized appropriate postoperative pain control will be enhanced by updated information on pharmacological and non-pharmacological pain management.

Keywords: Acute postoperative pain management, Clinical guidance, Clinical guidelines

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Introduction

Currently, approximately 80% of patients undergoing surgery experience moderate to severe pain in the postoperative period. In recent years there has been substantial improvement in the treatment of acute postoperative pain including implementation of new techniques, the use of new medications, and the use of multimodal, multiphasic analgesia as well as surgery-specific pain management.

Since the publication of the first Thai clinical guidance for management of acute postoperative pain in 2011, there have been significant improvements in acute postoperative pain management including new analgesics and the development of new techniques. There has also been a significant movement towards minimally invasive surgical procedures, coupled with an effective pain management strategy.

The objective of this guidance is to update clinicians on new developments and to provide evidence-based recommendations for acute postoperative pain and a brief update regarding clinical pharmacology of available analgesics in Thailand.

Methods

- Panel composition

From TASP and RCAT committee members, a panel of 13 members with expertise in anesthesia and pain management formulated the clinical guidance and recommendations for acute postoperative pain management set forth below. The chairman (ST) leaded the panel and finalized this guidance.

- Target audience and scope

The objective of this clinical guidance is to provide evidence-based recommendations for acute surgery-specific pain management. The target audiences are clinicians who manage postoperative pain. Management of chronic pain, acute nonsurgical pain, dental pain, traumatic pain, and periprocedural (nonsurgical) pain are outside the scope of this guidance.

- Evidence review and grading

The authors investigated and reviewed case-reports, primary studies, systematic reviews and recently published acute postoperative pain management guidelines as well as book chapters. A total of 182 publications were reviewed in the development of this guidance. Searches were udated through October 2018.

Evidence was graded based on previous grading strength of recommendations and quality of evidence in clinical guidelines[1], which stratified the grading into 1A: strong recommendation, high-quality evidence; 1B: strong recommendation, moderate-quality evidence; 1C: strong recommendation, low-quality or very low-quality evidence; 2A: weak recommendation, high-quality evidence; 2B: weak recommendation, moderate-quality evidence: and 2C: weak recommendation, low-quality or very low-quality evidence.

Recommendations

There are three phases of perioperative pain management; preoperative pain assessment/patient education (box 1), intraoperative anesthetic/analgesic plan and techniques (box 2) and postoperative pain management flow (box 3-11), as shown in the diagram 1.

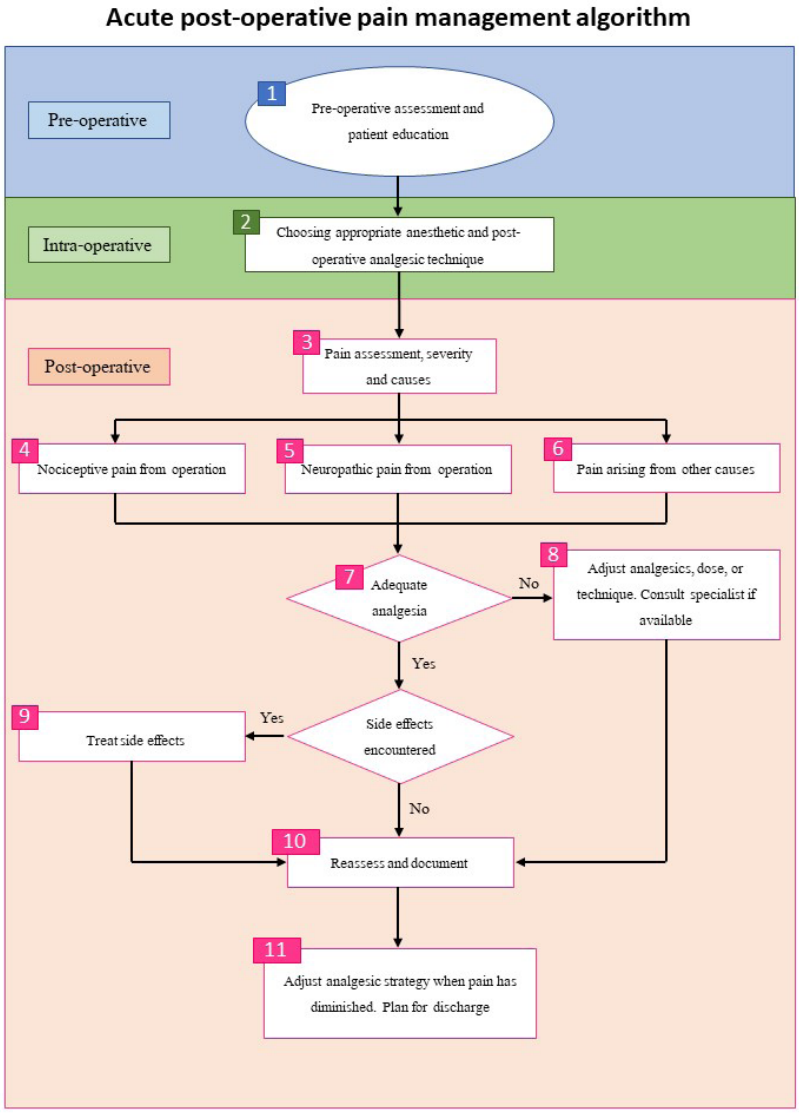

Diagram 1: Algorithm for peri-operative pain management

Box 1: Pre-operative assessment and patient education

Suggestion 1: Pre-operative assessment includes consideration of the type of surgical procedure, underlying disease, psychological and cognitive status, previous surgical history and analgesics received, history of chronic pain/ substance abuse, and concurrent use of other medications. In patients with pre-existing chronic pain, pain management should commence in the pre-operative period.

Efficient post-operative pain control requires planning throughout the perioperative phase. To achieve effective post-operative pain control, adequate communication between the anesthesia provider and the patient is of importance. Topics that should be discussed with the patient preoperatively include pain assessment methods, details of analgesic drugs, analgesic techniques, and the use of patient controlled analgesic delivery equipment (if in the plan). Any other concerns or questions that the patient might have should also be addressed at this time.

Suggestion 2: Patient/family-centered education together with tailoring pain management strategies to suit each individual is recommended. Patients and their families should be given information on choices of analgesic techniques/drugs and possible complications and side effects.

Suggestion 3: The chosen analgesic techniques and goals should be clearly documented for communication with the perioperative care team.

Box 2: Choosing the appropriate analgesic technique according to the type of surgery and anesthetic technique

Suggestion 4: Post-operative analgesia should be chosen in accordance with the expected trauma related to each surgical procedure (table 1) and ideally should be procedure-specific (table 2). Intra-operative anesthetic techniques should also be taken into consideration. The use of a multimodal approach should always be considered, for example, incorporating different analgesic drugs with different mechanisms of action such as paracetamol, NSAIDs, or opioids.

Table 1 Operations with varying degrees of expected post-operative pain[2]

Major trauma	Intermediate trauma	Minor trauma
Gastrectomy	Appendectomy	Minor urological procedures (transure-
Splenectomy	Laparoscopic procedures	thral prostatectomy, testicular surgery)
Liver/pancreatic surgery	Mastectomy	Circumcision
Esophageal surgery	Inguinal hernia surgery	Superficial surgery
Laparotomy/bowel resection	Vaginal hysterectomy	Examination under anesthesia
Laparotomy/cholecystectomy	Thyroidectomy	Anal fissure repair/anal stretch
Thoracic surgery	Ear, nose, throat surgery Adenoidectomy	Varicose vein surgery
Spinal fusion	Total hip replacement	Intraocular surgery
Renal surgery	Laparotomy/hysterectomy	
Total knee replacement	Cesarean Section	
	Hemorrhoidectomy	
	Extensive eye surgery	

BOX 3: Assessment of pain severity, cause of pain, and outcome of treatment

Suggestion 5: Appropriate pain assessment tools should be used. The patient's self-report of pain score is the most reliable. Widely used assessment tools/ methods of pain intensity by patient self-report include numeric rating scale (NRS), verbal rating scale (VRS) and visual analog scale (VAS). For patients with whom communication is difficult, a face pain assessment scale and behavioral pain assessment scale may be used instead[3].

Suggestion 6: After commencing post-operative analgesia, regular assessment should be made to determine the effectiveness of the analgesic regimen chosen for the patient. If post-operative pain is severe despite implementation of adequate multimodal analgesic regimen, causes for the abnormally unresponsive pain should be investigated, such as acute postoperative neuropathic pain, and appropriate measures to treat the pain should be initiated.

BOX 4: acute post-operative nociceptive pain[4-6]

Acute postoperative pain is most commonly somatic nociceptive inflammatory pain.

BOX 5: Acute postoperative neuropathic pain[7-14]

Acute postoperative neuropathic pain can develop from surgical trauma to the nerves. Patients with acute postoperative neuropathic pain may have the following clinical signs and symptoms[7,12-14]

1. Patients may describe pain with neuropathic characterisitcs such as burning, electrical shock-like, or radiating pain. Pain may be continuous or sporadic.
2. Patients may complain of paresthesia, such as numbness, tingling, or bugs crawling sensation.

3. Symptoms may occur in a clinically plausible distribution of the nerve that was damaged or injured.

4. This kind of pain does not typically respond well to conventional analgesics such as opioids, NSAIDs/COXIBs.

BOX 6: Pain from other causes

Other causes of pain in the postoperative period may be myofascial pain, migraine, neuropathic pain, gangrene, and surgical wound infection.

BOX 7: Outcome of pain control

Suggestion 7: After initiation of analgesic regimens, regular pain assessment should be made. The pain should be controlled in the mild level with a pain score of 4 out of 10 or 40 out of 100[15].

Suggestion 8: Apart from assessing pain scores, quality of life and functional outcomes should also be assessed as suggested by enhanced recovery after surgery (ERAS) recommendations. Functional aspects which may be evaluated include ability to walk or sit upright, abitlity to rest, quality of sleep, and emotional state.

Suggestion 9: Patient satisfaction should also be assessed and taken into account.

BOX 8: Dosage or technique should be adjusted according to severity of pain. Pain specialist consultation is helpful, if available.

Suggestion 10: We suggest using a multimodal approach to managing pain by using drugs which act on different mechanisms and utilizing their additive or synergistic effects to improve pain control, while minimizing side effects and dosage[16] (table 2). Effectiveness of pain relief should always be reassessed, tailored and adjusted to meet the needs of each individual patient. Patients with inadequate pain control may benefit from increase in dosage or decrease in dosing interval. The safety of drug delivery should also be assesed to ensure the right drug, the right dosage, the correct interval and the correct route of administration (table 3). An increase or decrease in the dosing interval may be required in patients who are already receiving around the clock or PRN analgesics but who are experiencing inadequate pain relief (diagram 2, 3).

Suggestion 11: Patients who are expected to have severe postoperative pain or pain that will be difficult to control perioperatively should be managed by a pain specialist according to a suitable plan, such as IV-PCA (intravenous patient controlled analgesia), CEA (continuous epidural analgesia), or peripheral nerve blocks.

BOX 9: Managing side effects and complications

Suggestion 12: A protocol for monitoring side effects and complications related to analgesics should be used. Side effects and complications from opioids can occur regardless of route of administration. Side effects from NSAIDs and opioids are listed in table 3 and 4.

Suggestion 13: A standing order for treating serious and common side effects or complications should be used. Treatment of side effects should be given as soon as possible.

BOX 10: Monitoring and documentation

Suggestion 14: Appropriate pain scores should be recorded as the 5th vital sign.

Suggestion 15: Analgesics and techniques should be adjusted or changed according to severity of pain.

Intravenous patient controlled analgesia

Patients who initially receive IV-PCA with morphine with a continuous infusion rate should have the continuous infusion stopped once pain has improved. Whenever patients are allowed to have oral fluid or meals, oral analgesics should be supplemented. If the patient does not require any demand doses from the PCA in 12 hours, the PCA should be stopped.

Epidural analgesia

Step-down analgesia with epidural catheter depends on the technique used

1. Epidural analgesia using an epidural catheter with a continuous infusion and patient controlled

epidural analgesia (PCEA) is considered the most effective analgesic technique. We recommend that this technique be used whenever possible. Continuous infusion and PCEA should be continued until the date on which postoperative pain is predicted to be minimal. If the catheter is kept for more than 3 days, signs of infection should be closely monitored (tenderness, erythema around the catheter).

2. The dosage of epidural morphine varies between 1-5 mg for every 12-24 hours. The dosage selected depends on catheter position, patient's age, underlying medical conditions, and history of previous opioid usage. Epidural morphine should not be used in patients with histories of severe side effects from epidural opioids.

3. Whenever oral intake is allowed, oral analgesics should be supplemented. Twenty-four hours after initiation of oral analgesics, cessation of epidural analgesia should be considered. If the surgical procedure is an upper abdominal procedure which is expected to produce severe postoperative pain or if the surgical incision is in the subcostal area, it may be reasonable to wait until postoperative day 3 before cessation of epidural analgesia. If in doubt, after the initial epidural analgesia has been completed, continuous epidural infusion can be temporarily stopped for 12 hours. If after 12 hours, the patient is not experiencing significant pain, the epidural catheter may be removed.

4. A bolus dose of morphine through the epidural catheter before removal of the catheter is not always necessary. Instead, the severity of postoperative pain, the number of postoperative days and the effectiveness of oral analgesics should be taken into account.

Pain management after cessation of IV-PCA/PCEA

A multimodal approach with oral or intravenous analgesics should always be considered in combination with IV-PCA and PCEA. We recommend that non-opioid analgesics, such as paracetamol, NSAIDs and nefopam should be prescribed if there are no contraindications.

Weak opioids (tramadol and codeine) should only be used if paracetamol fails to provide adequate pain relief. This group of analgesics are more suitable for pain at rest than incidental pain on movement. If side effects are encountered, we recommend switching to other analgesics.

BOX 11: If pain has decreased, adjust analgesic technique and plan for analgesia after discharge

Suggestion 16: Patients and care givers should be educated on the analgesics used once discharged

Suggestion 17: At home, analgesics should be taken promptyl if there is significant pain. It is not recommended that patients wait unitl the pain is severe before taking analgesics. If pain persists, then analgesics should be taken around the clock until it subsides. After that the patient may take analgesics on a PRN basis.

Conclusion

Each surgical procedure produces varying degrees of postoperative pain. A comprehensive and effective pain management strategy includes the continuous management in the preoperative, intraoperative, and postoperative perioids. Patients and their caregivers should be educated on the analgesics and the technique used. Analgesics should not be withheld until there is severe pain, instead it should be given early whenever there is significant pain. Pain should also be assesed on a regular basis during the perioperative period until the patient is discharged from the hospital.

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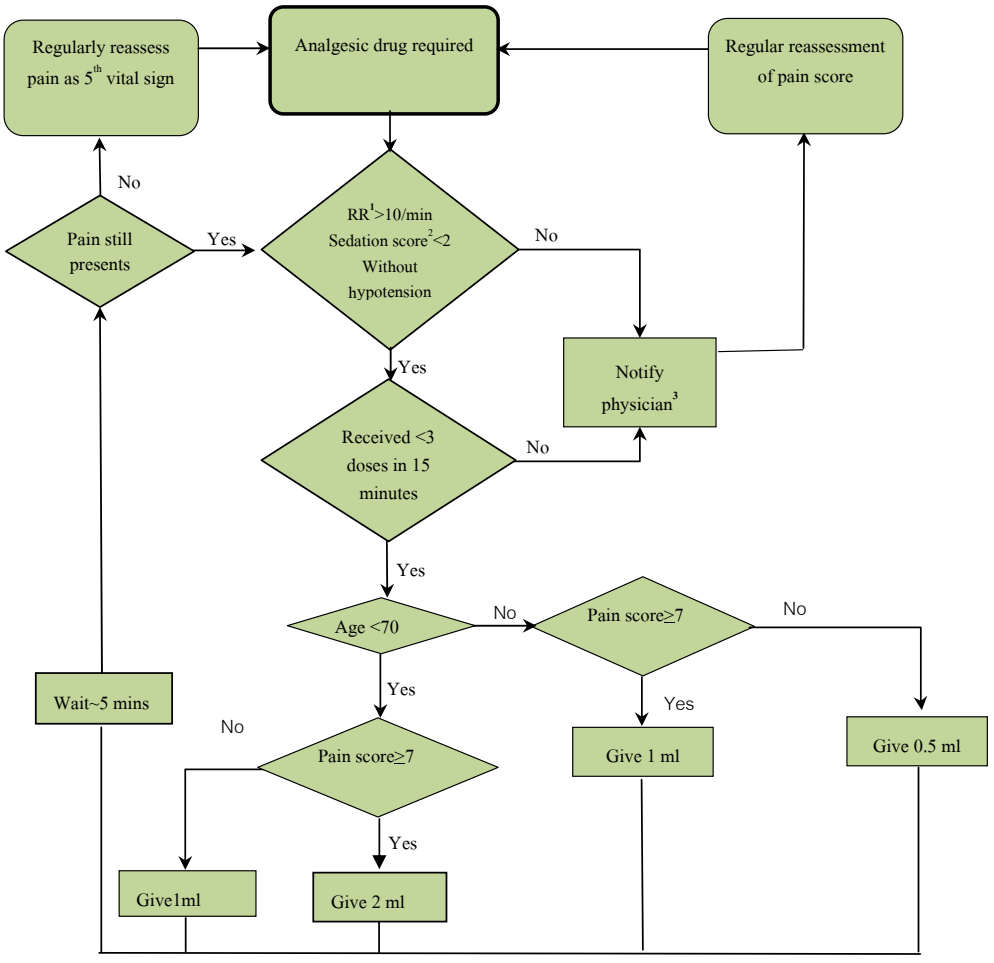
Diagram 2 : Opioid intravenous (IV) titration



Note:

Drug dilution:morphine as 1 mg/mL, pethidine 10 mg/mL, fentanyl as 10 mcg/mL

1.RR = respiratory rate potentially dangerous if below 10 breaths/ min

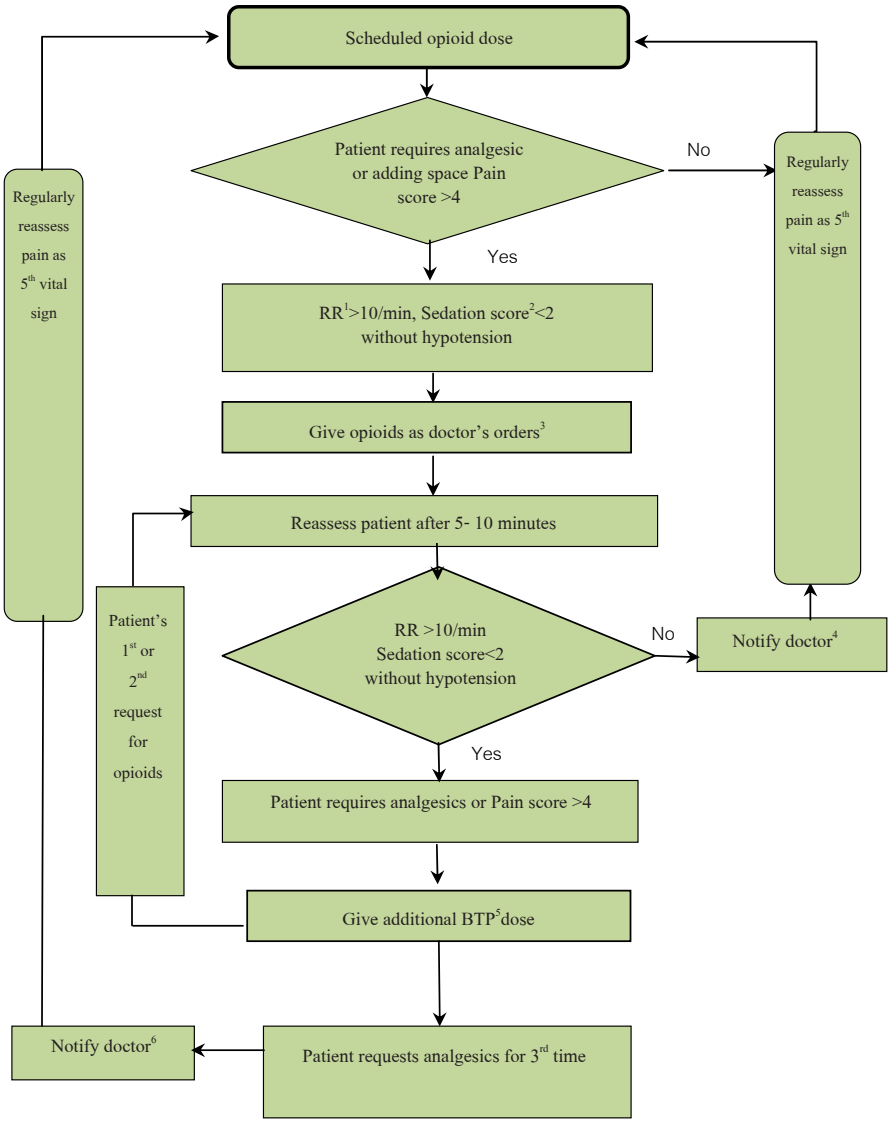
2. Sedation score (0-3; 0 = fully awake,1= drowsy, 2 =sedated but easily arousable, 3 = sedated and difficult to arouse,S= normal sleep)

3. Follow TASP recommendationswhile monitoring for and treating the following:

- Do not give the following scheduled dose
- Wait until Sedation score<2 andRR >10breaths/min
- Give supplemental oxygenor 0.1 mg IVnaloxone/dose

4. If pain persists, consider givingnon-opioidanalgesics. Treatment should be given for nausea and vomiting

Diagram 3: Administration of opioids around the clock



Note:

1.RR =respiratory rate. Potentially dangerous if below 10 breaths/min

2. Sedation score (0-3; 0 = fully awake,1= drowsy, 2 =sedated but easily arousable, 3 = sedated and difficult to arouse, S= normal sleep)

3.Orders for Morphine IV (scheduled, around the clock)
2mg q 2 hr, 3 mg q 3 hr, 4 mg q 4 hr
According to age, body weight, and severity of pain

4. Follow TASP recommendations while monitoring for and treating the following:

- Do not give the following scheduled dose
- Wait until Sedation score<2 and RR >10 breaths/min
- Give supplemental oxygen or 0.1 mg IV naloxone/dose
- Decrease opioid dosage 25% for next dose

5. BTP = break through pain (Pain that arises between scheduled doses, 25-50% of regular opioid dose may be given.)

6. Consider giving 3rd BTP dose,giving non-opioid analgesics or increase the next scheduled dose by 25 – 50%. Treatment should be given for nausea and vomiting.

Table 2 Options for components of multimodal analgesia for commonly performed surgeries

Type of Surgery	Systemic Pharmacologic Therapy	Local Infiltration Analgesia	Regional Analgesia	Neuraxial Analgesia	Non-pharmacologic Therapy
Open laparotomy colorectal surgery ± hepatobiliary surgery ± esophageal surgery[17-26]	-Opioids (1A) -Coxibs (1B) and/or paracetamol (1B) -Gabapentin (1B) or pregabalin (1B) -IV Lidocaine infusion (2B) -IV Dexmedetomidine (2B) -IV Nefopam (1B)	Continuous wound infiltration (1B)	TAP block (1B)	-Epidural local anesthetic with/without opioid; T6-12 (1B) -Intrathecal morphine; less than 0.3 mg (1B)	-
Laparoscopic colorectal surgery[161-174]	-Opioids (1A) -Coxibs (1B) and/or paracetamol (1A) -Gabapentin(1A) or pregabalin (2B) -IV Lidocaine infusion (1A)	Single shot wound infiltration (1B)	TAP block (1B)	-Intrathecal morphine (1B); 0.2-0.25 mg (age<75 years), 0.15 mg (age>75 years)	-
Open laparotomy (gynecologic/oncologic surgery)[27-47]	-Opioids (1A) -NSAIDs (1A)/Coxibs (1A) and/or paracetamol (1A) -Gabapentin (1A) or pregabalin (1A) -IV Nefopam (1B)	Single shot wound infiltration (1B)	TAP block when patients have undergone GA without neuraxial block (1B)	-Intrathecal morphine; 0.2 mg (1A) -Low thoracic epidural local anesthetic with/without opioids; T 10-12 (1A)	-Preoperative psychoeducational intervention (2B) -Intraoperative music (2B)
Laparoscopic cholecystectomy[48-66]	-Opioids (1A) -NSAIDs (1A)/Coxibs (1A) and/or paracetamol (1A) -Gabapentin (1A) or pregabalin (1A) -IV Lidocaine (1A) -IV Nefopam (1A)	Single shot wound infiltration (1B)	TAP block or subcostal TAP block (1A)	-	-Transcutaneous electrical nerve stimulation (TENS) (2B) -Music (2B)
Cesarean section[67-75]	-Opioids (1A) -NSAIDs (1A)/Coxibs (2A) -Paracetamol (1A)	Single shot/continuous wound infiltration (2B) for general anesthesia	TAP block (1B) or quadratus lumborum block (2B) when patients have undergone general anesthesia without neuraxial block	Intrathecal morphine (1A)	Music (2B)
Major spine surgery[76-84]	-Opioids (1A) -NSAIDs (1B)/ Coxibs (1A) and/or paracetamol (1B) Gabapentin (1B) or pregabalin (1B) -IV Ketamine (1B) -IV Dexmedetomidine (1B) -IV Nefopam (2B)	Single shot wound infiltration (1B)	Thoracolumbar interfascial plane (TLIP) block (1B)	-Intrathecal opioid (1B) -Continuous epidural infusion (1B)	-TENS (1B) -Music (1C) -Environmental management (1C)

Type of Surgery	Systemic Pharmacologic Therapy	Local Infiltration Analgesia	Regional Analgesia	Neuraxial Analgesia	Non-pharmacologic Therapy
Total hip replacement[85-102]	-Opioids (1A) -NSAIDs(1A)/ Coxibs (1A) and/or paracetamol (1A) -Gabapentin (1A) or pregabalin (1A) -IV Ketamine (2B)	Local infiltration analgesia (1A)	-Femoral nerve block (1B) -Fascia iliaca compartment block (1B)	Epidural local anesthetic with/ without opioid (1B), or intrathecal opioid (1B)	Cognitive modalities (1B)
Total knee replacement[103-115]	-Opioids (1A) -NSAIDs (1A)/ Coxibs (1A) and/or paracetamol (1A) -Gabapentin (1A) or pregabalin (1A) -IV Ketamine (2B)	Local infiltration analgesia (1A)	-Adductor canal block (1B) -Femoral nerve block (1B)	Epidural local anesthetic with/ without opioid (1B), or intrathecal opioid (1B)	-Cognitive modalities (1B) -Cooling and compression technique (1B)
Major breast surgery[116-131]	-Opioids (1A) -NSAIDs (1A)/Coxibs (1A) and/or paracetamol (1A) -Gabapentin (1A) or pregabalin (1A)	Continuous wound infiltration (2A)	-Paravertebral block (1B) -Pectoralis and serratus plane block (1B) -Intercostal nerve block (1B)	Thoracic epidural local anesthetics with/without opioids (2B)	-Music therapy (2C) -Transcutaneous electrical stimulation of acupoint (2C)
Open thoracotomy for lung surgery[132-155]	-Opioids (1A) -NSAIDs (1A)/Coxibs (1B) and/or paracetamol (1B) -Gabapentin (1B) or pregabalin (1B) -IV Ketamine (1B)	Single shot wound infiltration (1B)	-Paravertebral block (1B) -Intercostal nerve block (1B)	-Thoracic epidural local anesthetic with/without opioid (1B) -Intrathecal opioid (1B)	TENS (2B)
Video-assisted thoracoscopic surgery (VATS)[156-160]	-Opioids (1A) -NSAIDs (1B)/Coxibs (1B) -Paracetamol (1B)	Single shot wound infiltration (2B)	-Paravertebral block (1B) -Intercostal nerve block (1B)	-	-
Major neck reconstructive surgery[175-180]	-Opioids (1A) -NSAIDs (1A)/Coxibs (1A) and/or paracetamol (1A)	-	Bilateral superficial cervical plexus block (2B)	-	-

Grading system[1]

Strength of recommendation: 1=strong, 2=weak according to the balance among benefits, risks, burdens, and possibly cost, and the degree of confidence in estimates of benefits, risks, and burdens

Evidence quality: A = high quality evidence, B = moderate quality evidence, C = low or very low-quality evidence

GA= general anesthesia, TAP=transversus abdominis plane

Table 3 Details of analgesics for acute pain management

Drug	Indications	Cautions/contraindications	Side effects/adverse reactions	Adult dosage
A: Non-Opioids				
A1: Local anesthetics				
Bupivacaine	Amide group local anesthetic, Used for local infiltration, epidural and spinal anesthesia Duration of action 200-400 minutes	-Higher cardiotoxicity compared to other local anesthetics -Should not be used for IV regional analgesia	Toxicity: peri-oral tingling or numbness, agitation, tinnitus, seizure, cardiac arrest	-Infiltration/epidural: recommended 2 mg/kg every 4 hours -Maximum dosage depends on route/site given -0.25%-0.5% concentration is available in Thailand
EMLA (Eutectic Mixture of Local Anesthetics)	Cream containing 2.5% lidocaine + 2.5% prilocaine for topical application	-Absorption depends on site and duration of application -Should not be applied over wounds and mucous membranes	Potential for methemoglobinemia in patients with G-6-PD deficiency	Applied generously and cover for 1-2 hours before procedure
Levobupivacaine	Levorotatory (S) enantiomer of bupivacaine Less cardiotoxicity and neurotoxicity compared to bupivacaine	Same as bupivacaine	Same as bupivacaine	-Same as bupivacaine -Maximum dosage: 150 mg/dose or 400 mg/day -For postoperative analgesia, dosage should not exceed 18.75 mg/hour.
Lidocaine	-Amide local anesthetics, rapid onset -Duration of action 30-90 minutes -Addition of adrenaline can prolong duration of action	Preparations with adrenaline contains preservative	Toxicity: perioral tingling or numbness, agitation, tinnitus, seizure, cardiac arrest	-Available as 0.5%-2% solutions -Maximum dose depends on site of injection -3 mg/kg every 4 hours. -With adrenaline: 6 mg/kg. Every 4 hours For intravenous infusions; bolus 1-1.5 mg/kg, then infusion 1-2 mg/kg/hour until end of operation
Ropivacaine	Amide local anesthetics, Duration of action 8-24 hours.	Same as bupivacaine	Same as bupivacaine Less cardiotoxicity compared to bupivacaine Less motor blockade than bupivacaine and levobupivacaine	-Available as 0.2%, 0.5%, 0.75% and 1% solutions -Maximum dose is 2 mg/kg for regional anesthesia
A2: NSAIDs				
Celecoxib	NSAID that selectively inhibits cyclooxygenase-2 (COX-2) decreasing gastrointestinal side effects and platelet inhibition	Contraindicated in patients with -Sulfonamide allergies -Severe renal impairment -Gastric ulcers -Heart failure -Coronary artery disease -Cerebrovascular disease -S/P CABG/Stent -pregnant or lactating women	-Water retention -Acute renal failure in patients with pre-existing renal impairment or dehydration	-PO: First day give 400 mg followed by an additional 200 mg If required then 200 mg once or twice daily for the following days.

Drug	Indications	Cautions/contraindications	Side effects/adverse reactions	Adult dosage
Codeine	A weak opioid Used for mild to moderate pain	-	-Nausea and vomiting -Drowsiness -Confusion and agitation -Constipation	-PO: 30-60 mg every 4 hours -Maximum 240 mg/day
Diclofenac	Highly effective NSAID for mild to moderate pain	Contraindicated in patients with -Aspirin allergy -Asthma -Severe renal impairment -Gastric ulcers	-Inhibits platelet function -Causes gastrointestinal bleeding -Bronchospasm -Tinnitus -Water retention - May cause acute renal failure in patients with pre-existing renal disease or dehydration -Impairment of liver function	-PO: 25-50 mg every 8 hours -Deep IM: 75 mg once daily -IV infusion: For severe pain: give 75 mg IV infusion in 30-120 minutes. An additional 75 mg may be given 2-3 hours after previous dose For post-operative pain: 25-50 mg IV infusion in 15 - 60 minutes followed by 5 mg/hour -maximum of 150 mg/day -IV/IM should not be continued for more than 2 days. If required, a switch to PO is advised
Etoricoxib	NSAID that selectively inhibits cyclooxygenase-2 (COX-2) decreasing gastrointestinal side effects and platelet inhibition	Contraindicated in patients with -Sulfonamide allergies -Severe renal impairment -Gastric ulcers -Heart failure -Coronary artery disease -Cerebrovascular disease -Previous CABG or coronary stent -Pregnant or lactating women -Uncontrolled hypertension	-Water retention -Acute renal failure in patients with pre-existing renal impairment or dehydration	PO: 60-120 mg once daily 120 mg for acute pain should not be continued for more than 8 days
Ibuprofen	NSAID for mild to moderate pain with the least side effects compared to other NSAIDs	-Aspirin allergy -Asthma -Severe renal impairment -Gastric ulcers	-Inhibit platelet function -May cause gastric ulcers or upper GI bleeding -Bronchospasm -Tinnitus -Water retention - Acute renal failure in patients with pre-existing renal impairment or dehydration	PO: 400-800 mg for initial dose then 400 mg QID

Drug	Indications	Cautions/contraindications	Side effects/adverse reactions	Adult dosage
Ketorolac	NSAIDs for mild to moderate pain. Most pronounced platelet inhibition among NSAIDs Should not be used more than 5 days consecutively	-Aspirin allergy -Asthma -Renal impairment -Gastric ulcers -Concurrent anticoagulants, antiplatelets or any other condition impairing platelet function -Should not be used intraoperatively in cases with expected massive bleeding	-Inhibit platelet function -May cause gastric ulcers or upper GI bleeding -Bronchospasm -Water retention - Acute renal failure in patients with pre-existing renal impairment or dehydration	-Normal adult dosage 30 mg IV once daily or 30 mg IV every 6 hours (not exceeding 120 mg/day). Should be administered as a slow bolus taking more than 15 seconds. 60 mg IM once daily or 30 mg every 6 hours (not exceeding 120 mg/day) -Elderly (age ≥65 years), renal impairment or body weight ≤50 kg) 15mg IV every 6 hours (not exceeding 60 mg/day) 30 mg IM once daily or 15 mg IM every 6 hours (not exceeding 60 mg/day)
Naproxen	NSAIDs for mild to moderate pain	-Aspirin allergy -Asthma -Severe renal impairment -Gastric ulcers	- Inhibit platelet function -May cause gastric ulcers or upper GI bleeding -Bronchospasm -Tinnitus -Water retention - Acute renal failure in patients with pre-existing renal impairment or dehydration	PO: 250-500 mg twice daily
Parecoxib	-Pro-drug of valdecoxib -Selectively inhibits cyclooxygenase-2 (COX-2) decreasing gastrointestinal side effects and platelet inhibition - Used for post-operative pain. Should not exceed 3 days	-Allergies to sulfonamides or aspirin - Severe renal impairment -Gastric ulcer -Heart failure -Coronary artery disease -Cerebrovascular disease -Previous CABG or coronary stent -Pregnant or lactating women -Uncontrolled hypertension	-Water retention - Acute renal failure in patients with pre-existing renal impairment or dehydration	-IV/IM: Initial dose of 40 mg followed by 20-40 mg every 12 hours (not exceeding 80 mg /day)
A3: Nefopam				
Nefopam	Is a non-opioid, non-NSAID analgesic	-Patients currently receiving medications that increase serotonin such as MAOIs, SNRIs, SSRIs, TCAs, pethidine and tramadol. -History of convulsion	-Nausea vomiting -Tachycardia -Pain at site of injection	-IV infusion (15 minutes or longer): 20 mg every 4-6 hours not exceeding 120 mg/day
A4: Paracetamol				
Paracetamol	For mild to moderate pain	-Neonates -History of G-6-PD deficiency	Potential for hepatoxicity when exceeding recommended dose	-PO: 0.5-1 gm every 4-6 hours -IV (slow infusion): 0.5-1 gm QID not exceeding 4 gm/day

Drug	Indications	Cautions/contraindications	Side effects/adverse reactions	Adult dosage
Paracetamol 300 mg + codeine 15/30 mg	Please see “paracetamol” and “codeine”	Increasing the number of tablets taken could result in either drug within the combination exceeding daily maximum dose.	Please see “paracetamol” and “codeine”	Please see “paracetamol” and “codeine”
Paracetamol 350 mg + tramadol 37.5 mg	Please see “paracetamol” and “tramadol”	Increasing the number of tablets taken could result in either drug within the combination exceeding daily maximum dose.	Please see “paracetamol” and “tramadol”	Please see “paracetamol” and “tramadol”
B: Opioids				
Codeine 15/30 mg + paracetamol 300 mg	Please see “paracetamol” and “codeine”	Increasing the number of tablets taken could result in either drug within the combination exceeding daily maximum dose.	Please see “paracetamol” and “codeine”	Please see “paracetamol” and “codeine”
Fentanyl	A potent synthetic opioid with high lipid solubility. Exhibits cardiostability. Duration of action is 30-60 minutes	-Decrease dose in elderly -Respiratory depression -Epidural/spinal: pruritus and delayed respiratory depression	-Depresses respiration and cardiovascular system -muscle rigidity with high doses	-IV bolus: 0.001-0.005 mg/kg (can be titrated up to 0.05 mg/kg) -Epidural: 0.025-0.1 mg (diluted in local anesthetics or saline) -Spinal: 0.005-0.02 mg
Morphine	Opioid analgesic	-More likely to cause respiratory depression, pruritus, nausea, vomiting when given through the epidural or spinal route.	-Can trigger histamine release, causing hypotension and bronchospasm -Pruritus -Nausea vomiting -Confusion and agitation	-IV: 2-5 mg prn every 1-2 hours -IM/SC: 5-10 mg every 4 hours or prn every 2 hours (consider patient’s age, medical condition, and severity of pain when choosing dose) -Epidural: 2-4 mg (preservative free) -Spinal: 0.1-0.3 mg (preservative free)
Naloxone	Pure opioid antagonist -For reversal of respiratory depression caused by opioids -Low dose used for pruritus from epidural opioid -IM given in neonate’s whose mother has received opioids	-Duration of action 30 minutes -Potential for renarcotization when used to antagonize long acting opioids -Acute withdrawal in patients with physical dependence on opioid	-	-Slow titration until respiratory depression improves -IV bolus: 0.1-0.4 mg or 0.001-0.004 mg/kg Can be repeated every 2-3 minutes (duration of action 30 minutes) -For pruritus from epidural opioid: 0.1 mg Bolus (0.001-0.002 mg/kg)
Pethidine	Synthetic opioid for -Pain relief -Treatment for post-operative shivering -Biliary colic -Renal colic	-High doses may cause seizure -Patient receiving drugs that increase serotonin such as MAOIs, SNRIs, SSRIs, TCAs, nefopam and tramadol -Should not use in elderly patients	-Respiratory depression -Hypotension -Confusion and agitation -Myoclonus jerk	-IV: 20-50 mg prn every 2 hours -For post-operative shivering: 10-25 mg once -IM/SC: 25-100 mg every 3 hours or prn every 2 hours -Consider patient’s age, medical condition and severity of pain when deciding on dose

Drug	Indications	Cautions/contraindications	Side effects/adverse reactions	Adult dosage
Tramadol	-Believed to have less respiratory depression, constipation and less euphoric effects compared to other opioids -Acts both as a weak opioid and descending inhibitory pathway facilitator -Can be used to treat neuropathic pain	-Only 30% of effect is reversible with naloxone -Should not be used in patients with history of seizure -- Patient receiving drugs that increase serotonin such as MAOIs, SNRIs, SSRIs, TCAs, nefopam and pethidine	Nausea dizziness dry mouth	-PO: 50-100 mg every 4 hours -IV/IM slowly 50-100 mg every 4 hours -Do not exceed 400 mg/day
Tramadol 37.5 mg +paracetamol 325 mg	Please see “paracetamol” and “tramadol”	Increasing the number of tablets taken could result in either drug within the combination exceeding daily maximum dose	Please see “paracetamol” and “tramadol”	Please see “paracetamol” and “tramadol”
C: Adjuvants				
Gabapentin	Use as adjuvant in neuropathic pain with other analgesics for additive effect	Excreted unchanged in urine. Dose adjustment required in renal impairment	-Marked drowsiness, dizziness -Edema and water retention	-300-1200 mg single dose 2 hours prior to surgery -No consensus on how long to continue after surgery
Ketamine	Phencyclidine derivative. Causes dissociative anesthesia Should be used only by specialists	-Hypertension -Agitation -Hypersalivation	-Hypertension -Increases intracranial pressure -Increase uterine contraction -Hypersalivation -Respiratory depression when given rapidly	-For pain: 0.05-0.1 mg/kg/hour infusion along with opioids
Pregabalin	Use as adjuvant in neuropathic pain with other analgesics for additive effect	Excreted unchanged in urine. Dose adjustment required in renal impairment	-Marked drowsiness, dizziness -Edema and water retention	150-300 mg single dose 2 hours before surgery

Note:

-OD = once daily, bid = twice daily, tid = three times daily, qid = four times daily, prn = as needed

-PO = per oral, PR = per rectal, SC = subcutaneous, SL = sublingual, IM= intramuscular, IV= intravenous

-MAOIs = monoamine oxidase inhibitors, SNRIs=serotonin norepinephrine reuptake inhibitors, SSRIs=selective serotonin reuptake inhibitors, TCAs, = tricyclic antidepressants

-Some medications given per rectally are not available in Thailand

-When choosing analgesics, specific circumstances and resources available in certain situations should be taken in consideration. The recommendations above may be deviated from as appropriate

Table 4 Adverse reactions and side effects from opioids[181-182]

Signs/Symptoms	Risk factor	Evaluation	Treatment	Medication
Respiratory depression/ Sedation	Opioid naive, Small children and the elderly, Pre-existing respiratory disease, Obesity, Obstructive sleep apnea, Concurrent use of other sedative drugs	Respiratory rate < 10 / min, Sedation score > 2	Give supplemental oxygen and open airway. Consider naloxone bolus with infusion for patients who received long acting opioids such as intraspinal morphine (duration of action for naloxone is 30-60 minutes)	-Naloxone IV 0.04-0.2 mg every 2-3 minutes until patient is awake or respiratory rate has returned to normal without rebound pain -Naloxone infusion: 2-5 mcg/ kg/hour according to clinical response.
Hallucination/ delirium/ cognitive failure	High dose, Depression, History of drug abuse, Elderly, Pre-existing cognitive impairment, Impaired liver/ renal function	Other causes for delirium have been ruled out (such as increased intracranial pressure, hypoxemia, infection, dehydration, abnormal metabolism), side effects from other drugs (such as chemotherapy, steroids, anticholinergics)	-Decrease dosage -Opioid rotation -Major or minor tranquilizers	Haloperidol 2-5 mg IM every 4-8 hours
Rigidity/ myoclonus/ seizures	High dose, Pre-existing epilepsy, Neurotoxicity from M3G, norpethidine, or tramadol		Opioid rotation to other opioids with inactive metabolites	-Lorazepam PO 0.5-1 mg OD - BID -Clonazepam PO 0.5-1 mg OD - BID -Baclofen 10 mg BID - TID
Nausea/ vomiting	-Patient: Female, non-smoking, history of nausea/ vomiting, car or sea sickness -Anesthetic technique: general anesthesia, nitrous oxide, use of opioids -Surgical: Duration and procedure such as laparoscopy, ear-nose-throat, neurosurgery, breast, strabismus, laparotomy, plastic surgery	Rule out other causes of nausea/ vomiting such as dehydration	-Pre-emptive antiemetics, -Opioid rotation if failure to respond to treatment	As needed (prn) anti-emetics. Around the clock if nausea/ vomiting is severe If risk factors are present, -use 2 anti-emetics together -Ondansetron (0.1 mg/kg) 4-8 mg IV every 6-8 hours (not exceeding 8 mg every 8 hours) -Dexamethasone 4-10 mg IV every 6 hours -Dimenhydrinate (1-2mg/kg) 50 mg PO prn every 6 hours -Metoclopramide (0.1-0.2 mg/ kg) 10 mg IV every 6-8 hours
Pruritus			Opioid rotation if failed to respond to treatment	-Diphenhydramine 25-50 mg PO every 6 hours Ondansetron 4 mg IV every 6 hours or 8 mg IV every 8 hours Naloxone 0.001-0.002 mg/kg IV titration according to clinical response
Urinary retention	Common with neuraxial opioid	Evaluate for full bladder and urinary voiding 1-2 hours postoperatively	Cold pack, consider catheterization if full bladder or retain catheter if continuous epidural analgesia given	Naloxone 0.001-0.002mg/kg IV titrate according to clinical response
Constipation		Pass stool less than twice/week	-Stool softener -Stimulant laxative -Osmotic agents -Saline cathartics	-Senokot 1-4 tablets hs -Bisacodyl 1-2 tablets hs -Lactulose 30 ml hs -Milk of magnesia 30 ml hs-tid

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