

Expert Consensus on Perioperative Medication Therapy Management within Enhanced Recovery After Surgery (ERAS) Programs

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Enhanced Recovery After Surgery (ERAS) refers to a series of optimized clinical pathway with evidence-supported medical evidence adopted during perioperative period, so as to reduce the psychological and physiological stress reactions of patients during perioperative period, decrease the incidence of postoperative complications, shorten hospital stay, and reduce medical expenses.

ERAS has developed rapidly in theory and application in recent years, and its implementation follows multi-disciplinary team (MDT) including surgery, anesthesia, pharmacy, nursing, rehabilitation, nutrition and psychology. The team members include doctors, pharmacists, nurses, therapists and nutritionist. It has been reported that at least 50% of surgical patients need long-term or short-term use of drugs^[1]. Perioperative pain, nausea and vomiting, anticoagulation, anti-infection, blood pressure management, blood glucose management, nutrition management, fluid management and other aspects are all involved in medication therapy, at the same time, it will cause medication related problems (MRPs) during perioperative period. At present, pharmacists have played an increasingly important role in the management of perioperative drug therapy. However, there is no unified guidance on the specific working mode of medication therapy management for pharmacists participate in ERAS programs. This consensus focuses on the dimensions from which pharmacists can fully participate in perioperative medication therapy management in ERAS team, collaborate on multidisciplinary comprehensive diagnosis and treatment, and optimize related medication therapy pathways.

1 Objectives of perioperative ERAS medication therapy management

Surgery is a process of repair in trauma for patients. The patient's physical condition, surgical process, perioperative stress and inflammatory reaction may lead to organ dysfunction, disease or surgical complications, and then affect the degree and speed of postoperative rehabilitation. In this regard, ERAS perioperative medication therapy management should be adopted, which includes not only comprehensive assessment of patients' drug-related needs, but also optimization of patients' perioperative medication therapy pathway, evaluation of drug efficacy, monitoring of adverse reactions, follow-up and medication education. It is integrated with the multidisciplinary integrated diagnosis and treatment mode, which ultimately reduces the incidence of postoperative complications, improves the quality of life of patients and shortens the length of hospital stay.

2 Working mode of clinical pharmacists in perioperative ERAS programs

2.1 Perioperative medication management principles of ERAS

2.1.1 Pharmacists should obtain the complete medication history of patients, especially those with chronic diseases with polypharmacy, identify the types and exact dosage of drugs used, including all prescription drugs, over-the-counter drugs, Chinese herbal medicines and health products, and find out whether the patients smoke or drink alcohol, and whether drugs that have an impact on perioperative period are involved. Pharmacists should evaluate the patient's medication and identify potential drug treatment problems.

2.1.2 Pharmacists should observe the efficacy and adverse reactions of drugs, and analyze the factors that may affect the metabolism of drugs in vivo and the body's elimination capacity while taking into account the pathophysiology of patients at that time, so as to discuss the individualized medication plan and monitoring.

2.1.3 Pharmacists should determine whether the drugs used by patients for a long time should be continued or reduced in the perioperative period, as well as the timing, dosage and the way of re-use after surgery, and whether adjustments are needed.

2.1.4 Pharmacists should determine whether short-term use of drugs in perioperative outpatient department, preoperative ward, intraoperative anesthesia operating room and postoperative ward will cause allergy, and consider the interaction between drugs.

Clinical pharmacists should recommend and discuss the use of drugs before and after operation based on

the patient's medical history, medication history, preoperative status, specific procedure of surgery, and postoperative situation, so as to achieve the optimal perioperative medication plan and rapid postoperative recovery, shorten hospital stay and reduce medical expenses.

2.2 Responsibility of pharmacists in ERAS during perioperative period

ERAS is a complete diagnosis and treatment process that runs through pre-admission, pre-operation, intro-operation, post-operation and after discharge, and its core is to emphasize the concept of patient-centered diagnosis and treatment. The main responsibility of clinical pharmacists in ERAS team is to formulate clinical drug treatment strategies, and carry out rational drug-based pharmaceutical treatment management centering on patients. Clinical pharmacists should optimize the medication treatment management pathway related to the core elements of ERAS, such as analgesia, nutrition, postoperative nausea and vomiting, anticoagulation, anti-infection, blood pressure, blood glucose, body fluid management, etc., as well as pharmaceutical evaluation and monitoring of patients with basic diseases, so as to promote the recovery of patients.

2.3 Starting line for clinical pharmacists in perioperative ERAS medication therapy management

2.3.1 Prediction of preoperative drug modification and problems associated with drug therapy

Pharmacists should conduct pharmaceutical consultation when patients are pre-hospitalized/admitted to hospital, so as to obtain complete medication history and allergy history, including medication purpose, drug name (generic name and trade name), specifications, usage and dosage, medication course, etc.; collect and analyze the medication list, and compare the patient's previous medication with the pre-surgery prescribed medication; consider the need to discontinue the use of drugs, drug interactions, repeated medication, etc.; analyze the patient's pharmacokinetics while restructuring and simplifying the prescription, and make the medication intervention and suggestion list for ERAS team members; clarify the content of perioperative drug monitoring, and formulate detailed monitoring plans.

2.3.2 Implementing standardized medication treatment path of ERAS

As a member of ERAS team, pharmacists should draw up the list of therapeutic drugs related to common operations in the surgical department where he/she works; adjust individually the process of medication therapy management and focus monitoring according to different diseases, types of operations, special populations and other factors; work with doctors to develop the entire ERAS medication therapy plan and working pathway suitable for the hospital. In addition, pharmacists can consult and train ERAS team on drug safety, drug interactions, adverse drug reactions and drug use characteristics in specific populations. At the same time, pharmacists should evaluate the efficacy of medication therapy, and improve the team's medication therapy in the implementation of ERAS.

2.3.3 Medication education and follow-up after discharge

Postoperative patients should be provided with medication education, and information should be collected in the follow-up in terms of the efficacy of medication, adverse reactions and medication compliance according to each patient's disease type, postoperative category and key drugs used. Coherent but individualized follow-up plans and forms should be developed according to specific diseases and medications.

3 The specific working path of ERAS pharmaceutical treatment management

Perioperative medication management of ERAS requires clinical pharmacists to participate in pharmaceutical evaluation, medication reconciliation, pharmaceutical care, medication education and training. Therefore, pharmacists' participation in ERAS pharmaceutical treatment management can be divided into five stages: Stage I: pre-admission/outpatient pharmaceutical care; Stage II: preoperative pharmaceutical evaluation and service; Stage III: intraoperative pharmaceutical care; Stage IV: postoperative pharmaceutical reevaluation and care; Stage V: postdischarge medication education and follow-up. See Figures 1-3 for specific working paths.

3.1 Pre-admission/out-patient pharmaceutical care

Before the patient is admitted to the hospital, the pharmacist should inquire about their medication history in detail, conduct pharmaceutical evaluation and generate pre-evaluation records in the preoperative diagnosis center, preoperative MDT clinic or pharmacy clinic, taking into account the actual conditions of the hospital. At this stage, pharmacists should screen the information of patients' past medication, including

drugs for main diseases, drugs for the combined with chronic diseases or self-administered drugs and healthy food. For those who have no history of chronic diseases, no history of long-term medication, and no correlation between short-term medication in perioperative period and ERAS drug treatment plan, pharmacists should carry out relevant perioperative medication education; If the patient's long-term medication or self-administration drugs involve the drugs in the perioperative drug list (attached table), including cardiovascular drugs, respiratory drugs, anticoagulant/antiplatelet drugs, digestive drugs, glucocorticoids, hypoglycemic drugs, rheumatological immune drugs, tumor targeting drugs, Chinese herbal medicines and self-administration drugs, etc., pharmacists need to restructure and simplify the pre-operation drugs according to specific conditions, and make pharmaceutical recommendations of individual therapy with ERAS short-term agreement drug drug treatment plan, and generate pre-evaluation records; The pre-evaluation is fed back to ERAS team to determine the next step through clinical comprehensive evaluation .

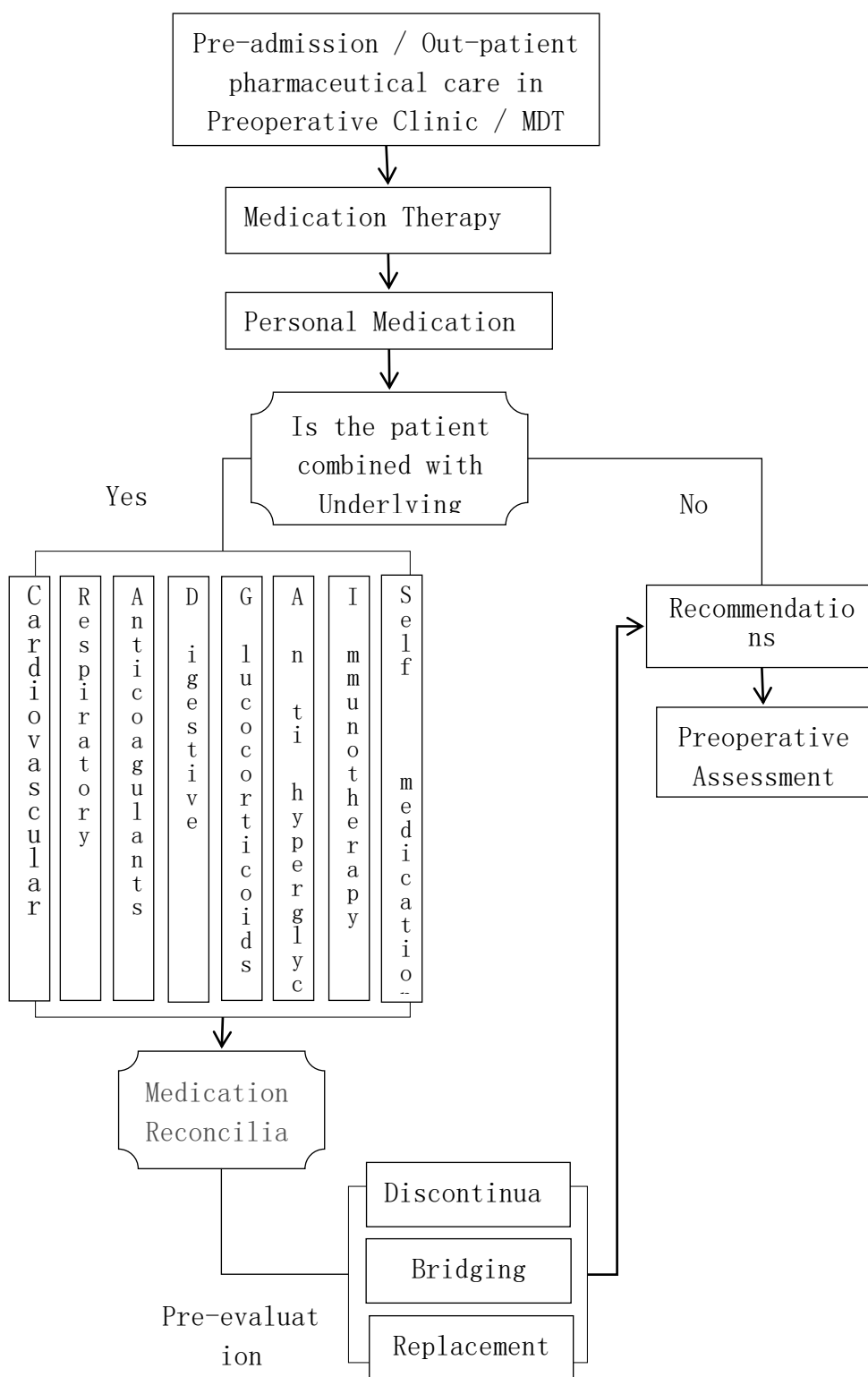


Figure 1. Work path of pre-admission/outpatient pharmaceutical care

3.2 Preoperative pharmaceutical evaluation and service

Preoperative pharmaceutical evaluation is aimed at patients admitted to hospital for elective surgery after outpatient evaluation, and is included in the whole process management of ERAS. The key points of

preoperative pharmaceutical care include: (1) Preoperative medication education for patients during perioperative period; (2) Review the medical orders based on outpatient pharmacy pre-evaluation records to ensure the correct implementation of medication reconciliation; (3) In case of high risk in preoperative evaluation, suggest individualized medication intervention plan to ERAS treatment team before surgery, and optimize ERAS drug medication plan.

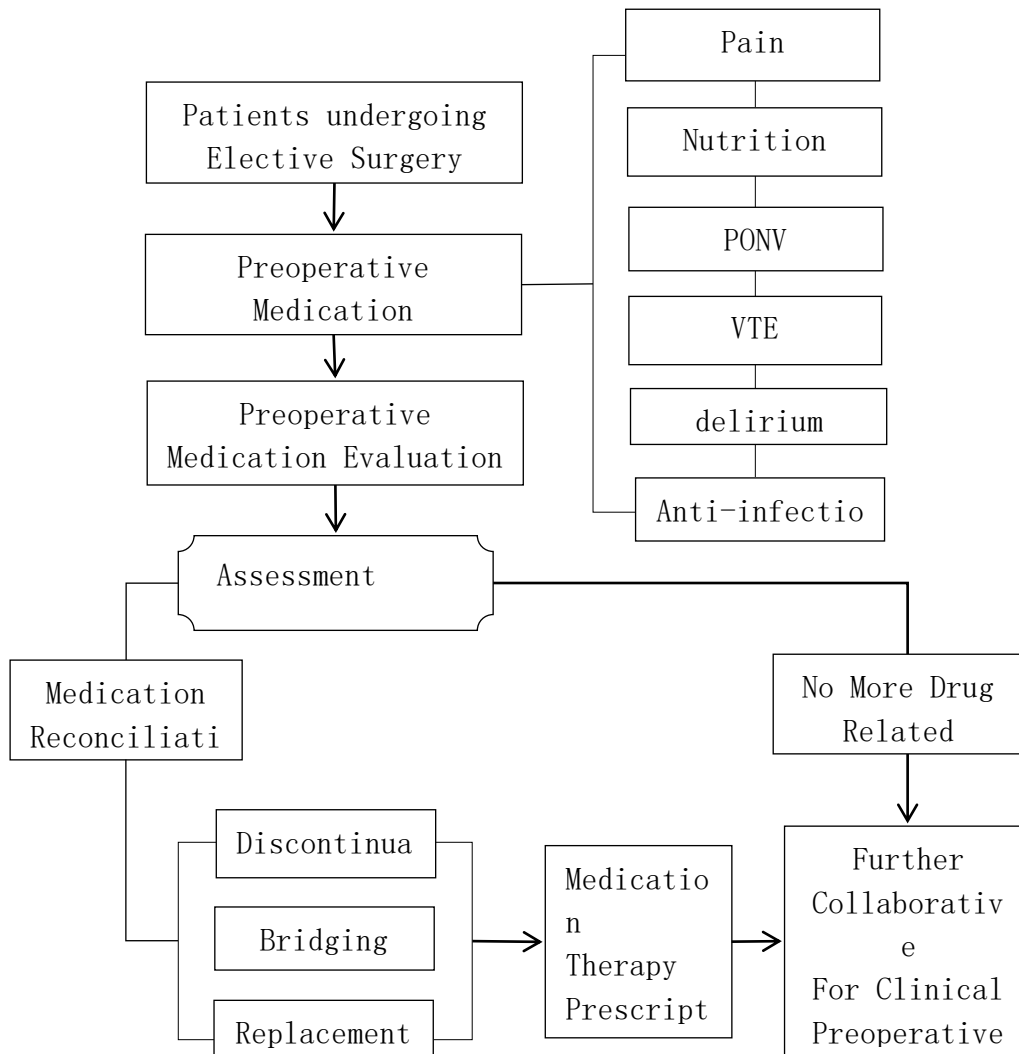


Figure 2 Preoperative pharmaceutical evaluation and service path

3.3 Intraoperative pharmaceutical care

The patients are typically in the operating room under anesthesia during surgery, and the key points of pharmaceutical care during the operation include: (1) Appropriate indications, varieties, timing and addition of antibiotics in the operating room; (2) Intraoperative drug interactions, drug compatibility and adverse drug reactions, focusing on monitoring analgesic drugs, application of analgesic pump, airway management and balance of water and electrolyte; (3) Review the medical orders after operation and the factors of adverse events related to drugs.

3.4 Postoperative pharmaceutical re-evaluation and monitoring

Patients need to be re-evaluated after surgery. Drug monitoring includes the assessment of postoperative pain, nausea and vomiting, nutritional status, venous thromboembolism, infection prevention and treatment, etc., and the reasons for poor efficacy, safety, compliance and execution accuracy of ERAS medication therapy are analyzed. After the operation, the drugs are reconciled, and the drug treatment effect, adverse reactions, drug interactions and drug use in special populations are monitored dynamically.

3.4.1 Postoperative pain assessment

Patients should be evaluated for pain intensity after the operation, such as visual analogue scale, numerical rating scale, language rating scale, and Wong-Baker facial expression rating scale., and need to evaluate the effect of the given analgesic regimen and adjust the analgesic regimen if necessary. Based on the results of pain assessment and surgical conditions, analgesia regimens can be developed, and prophylactic analgesia and multimodal analgesia can be adopted to achieve rapid postoperative recovery. Multimodal analgesia regimens include acetaminophen or other NSAIDs combined with opioids or tramadol, acetaminophen combined with one other NSAIDs and opioids or tramadol, and systemic analgesics (NSAIDs with or without opioids or tramadol) combined with local anesthetics for nerve block. Clinical pharmacists and doctors jointly formulate postoperative analgesia plans, dynamically evaluate the effects of drugs used by patients, participate in the adjustment of the dosage and types of analgesic drugs, and monitor adverse drug reactions.

3.4.2 Evaluation of postoperative nausea and vomiting

Patients should be evaluated for the curative effect of the postoperative nausea and vomiting (PONV) prevention program formulated before operation, and the nausea and vomiting after operation should be closely observed. If the preoperative prevention fails, the drug type can be changed to treat nausea and vomiting according to the risk factors, or the combination therapy can be considered for treatment.

3.4.3 Evaluation of postoperative nutritional status

According to preoperative screening and evaluation of patients' nutrition, including weight, BMI, NRS2002 score, PG-SGA, SGA and other scales, metabolic indicators, electrolytes, blood glucose, blood lipids, etc. during the use of nutritional preparations, the functions of liver, kidney and respiratory organs, the position of pipeline and tolerance/nutrition related complications, as well as the body fat and muscle content, grip strength, protein level and nitrogen balance should be monitored. The body protein, plasma albumin, prealbumin and transferrin levels should be evaluated, and the nutrition support methods and programs can be adjusted according to the evaluation with the corresponding adverse reactions of enteral and parenteral nutrition being monitored and dealt with.

3.4.4 Evaluation of postoperative venous thromboembolism

The coagulation parameters of patients should be monitored dynamically, and the postoperative bleeding observed. It is necessary to fully evaluate before using low molecular weight heparin, adjust drug dosage according to weight, renal function, coagulation parameters and bleeding, and comprehensively evaluate the patients' conditions to determine the duration of postoperative anticoagulation and the timing for patients with underlying diseases to resume preoperative anticoagulation/antiplatelet drugs.

3.4.5 Prevention and treatment of postoperative infection

The indications, timing, varieties, usage and dosage of drugs used to prevent infection in patients before and during operation should be reviewed, and the risk factors of nosocomial infection and multi-drug-resistant bacteria infection in patients after operation, as well as the preventive effect of prophylactic drugs, and the clinical manifestations and infection indicators of common infections such as incision, surgical site, lung and urinary tract after operation should be monitored. Breakthrough infection should be found in time and medication should be guided by PK/PD principle.

3.4.6 Postoperative medication reconciliation

For patients taking multiple drugs, doctors and clinical pharmacists should comprehensively evaluate the postoperative recovery and the original disease of patients and realize medication reconciliation. Pharmacists should suggest the timing for drug resumption, whether to adjust drug variety, dosage and administration methods. Meanwhile, clinical pharmacists should monitor drug interactions and adverse drug reactions, and educate patients on drug use.

3.5 Medication education and follow-up after discharge

Medication education for postoperative patients can be provided according to the type of disease, operation type and drug use, and follow-up time. A plan can be set according to the disease and drugs prescribed, and follow-up can be in the form of mobile application, pharmaceutical outpatient service, follow-up information system, telephone, email and others.

3.5.1 Medication education

Medication education for postoperative patients can be carried out according to the types of diseases, types of operations and drugs used. In principle, the following points can be included: (1) Regular and quantitative medication according to the medical orders; (2) Record the daily situation; (3) Medications that need to be taken for a long time, such as nutritional preparations and analgesics, need to be evaluated regularly; (4) Regular outpatient review; (5) Feedback possible adverse reactions during drug use; (6) Other precautions, such as diet, exercise and psychological adjustment.

3.5.2 Patient follow-up

Follow-up can be carried out in combination with mobile application, pharmacy clinic, follow-up information system, telephone, mail and others, the content of which includes: (1) Establishing the health records of patients undergoing surgery, including the basic information of patients, operation time, operation type, current medication and other important indicators; (2) Evaluating the patient's medication compliance, and confirm whether there are new medication problems; (3) Determining the possible adverse drug reactions and related review indicators for reexamination: routine blood and urine tests, liver and kidney function tests, etc.; (4) Setting the follow-up time and form according to the diseases and drugs taken. Follow-up should be strengthened for patients involved in organ transplantation, malignant tumor and chronic diseases.

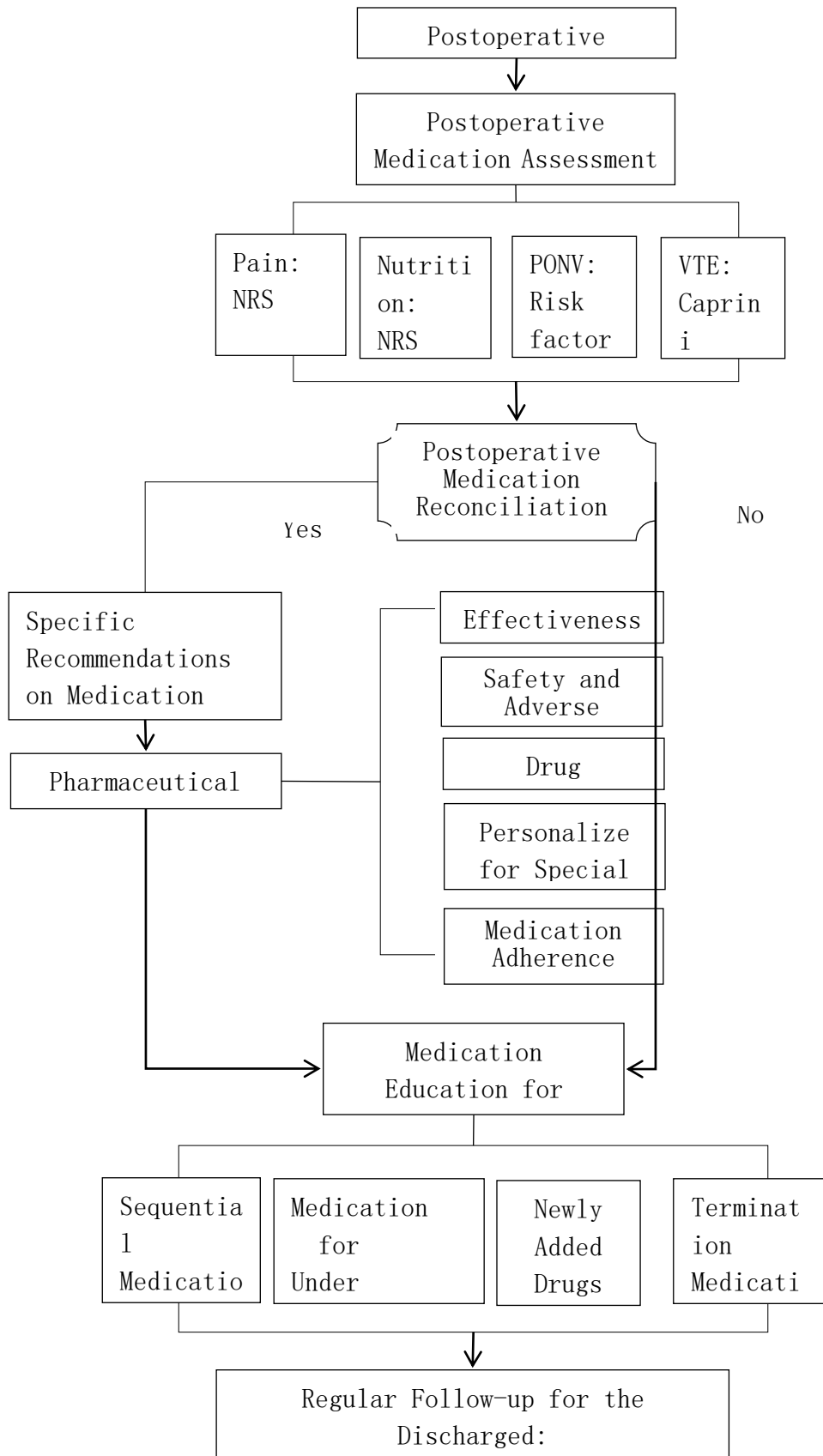


Figure 3 Postoperative pharmaceutical reassessment and monitoring path

4 Key points of medication monitoring for clinical pharmacists in perioperative medication management of ERAS

4.1 Cardiovascular drugs

Perioperative cardiovascular drugs mainly involve maintaining blood pressure and cardiac function. For elective surgery, the advantages and disadvantages should be weighed to reduce the adverse effects of perioperative drug adjustment on long-term medication patients.

4.1.1 β receptor blockers

Perioperative use of β receptor blockers has the potential benefit. It can reduce myocardial oxygen consumption by antagonizing the excitatory effects of neurotransmitters and catecholamines on β -receptors, and can prevent or control arrhythmias. Sudden discontinuation of β receptor blockers in patients with long-term use may increase the risk of myocardial ischemia, complications and even mortality^[2]. For patients with indications of drug use, including a history of hypertension, atrial fibrillation, angina pectoris, heart failure, and myocardial infarction, β receptor blockers are recommended to continue to be used during the perioperative period and throughout the hospitalization period, but the dosage should be adjusted during the perioperative period to achieve optimal maintenance of blood pressure and heart rate. At present, there is no definite conclusion on whether β receptor blocker should be used to prevent myocardial ischemia in patients with coronary heart disease during perioperative period. Prophylactic use of β receptor blockers for noncardiac surgery is not recommended to improve postoperative outcomes. β receptor blocker should be initiated in patients undergoing non-cardiac surgery, and should not be initiated 2-4 hours before surgery^[3].

If patients cannot take drugs orally, intravenous forms of β receptor blockers, including metoprolol, propranolol and labetalol, can be selected. Compared with non-selective β receptor blockers, selective β_1 receptor blockers have less effect on pulmonary and peripheral vascular responses. However, patients who have been using non-selective β receptor blockers for a long time do not need to be replaced with selective β_1 receptor blockers during perioperative period.

4.1.2 Calcium channel blockers

There is limited data on the risks and benefits of perioperative calcium channel blocker, and the available evidence theoretically suggests a benefit of calcium channel blocker use during perioperative period^[4]. Studies have proved that the reduction of mortality in patients undergoing cardiac surgery is related to the continued use of calcium channel blockers. In addition, a meta-analysis shows that the use of calcium channel blockers is related to the reduction of ischemia and atrial arrhythmia in patients undergoing non-cardiac surgery^[5, 6]. There is no significant drug-drug interaction between calcium channel blockers and the narcotic drugs mentioned in this article^[7], and the withdrawal reaction is not obvious after drug withdrawal. It is suggested that patients who have already started using calcium channel blockers before surgery should continue to use them during perioperative period. Most oral calcium channel blockers are long-acting sustained-release preparations, and short-acting preparations can be diltiazem and verapamil. Because short-acting nifedipine can quickly lower blood pressure, it should be avoided during perioperative period.

4.1.3 RASS inhibitors (ACEI and ARB)

Perioperative use of ACEI and ARB drugs is controversial. ACEI and ARB can reduce the compensatory activation of RASS system during surgery and prolong the duration of hypotension. The effects of ACEI and ARB are different in cardiac surgery, non-cardiac surgery and different anesthesia methods. Most studies on preoperative use of ACEI and ARB drugs show an increased risk of perioperative or postoperative hypotension and vascular shock.

Preoperative discontinuation of ACE inhibitors is recommended based on indications, patients' blood pressure, operation types and anesthesia methods. For most patients, drug discontinuation is usually recommended on the morning of surgery. However, for patients with refractory hypertension and heart failure, they can be used after weighing the advantages and disadvantages to avoid the deterioration of their condition. It is suggested that the use of ACEI should be resumed as soon as possible after surgery. Studies have shown that the failure to resume ARB use within 48 hours after surgery is associated with increased mortality within 30 days. You can refer to the published guidelines for the use of ACEI and ARB in the perioperative period^[8-10].

4.1.4 Diuretics

The main adverse effects of loop diuretics and thiazide diuretics on the body are hypokalemia and hypovolemia. Hypokalemia can increase the risk of perioperative arrhythmia, and reduce the effect of muscle relaxants during anesthesia to cause paralytic intestinal obstruction. In patients who use diuretics, vasodilation of narcotic drugs may induce hypotension. However, studies have shown that the use of furosemide on the day of surgery does not increase the incidence of hypotension during surgery in patients who have been treated with furosemide for a long time undergoing non-cardiac surgery^[11].

The use of diuretics during perioperative period depends on the purpose of medication and the patient's medical history. It is suggested that patients who use diuretics as antihypertensive therapy should stop taking them in the morning of the day of surgery. For patients who use diuretics for the treatment of heart failure, the perioperative drug use should be determined according to the assessment of the status of systemic circulation volume. For patients with stable circulating blood volume and well-controlled symptoms of heart failure, it is usually recommended to stop using diuretics on the morning of surgery. For patients with heart failure with poorly controlled symptoms and volume overload, it is recommended to continue the use of diuretics during perioperative period. The changes of blood potassium and volume should be paid close attention to in patients who need diuretics during perioperative period.

4.1.5 Lipid-lowering drugs

Evidence has shown that statins can reduce the incidence of cardiovascular events during perioperative period. For patients who take statins for a long time, it is recommended to continue to use them during perioperative period. For patients with indications and no previous use of statins, it is recommended to start statins treatment as early as possible before surgery if elective or emergency surgery is needed^[12].

Non-statin lipid-lowering drugs, including nicotinic acid and fibrotic acid derivatives (gemfibrozil and fenofibrate), can cause myopathy and rhabdomyolysis. When they are combined with statins, the incidence rate will increase, and surgery will also increase the risk of myopathy^[13]. Since these drugs have the effect of reducing the incidence of long-term vascular disease, it is safe to stop taking them, and it is recommended to stop taking them 1 day before surgery and suspend their use during perioperative period.

4.1.6 Digoxin

The related research data of perioperative digoxin use are limited. Indications for the use of digoxin include reducing the rate of hospitalization and readmission in patients with left ventricular dysfunction, and controlling ventricular rhythm during atrial fibrillation. It is suggested to continue to use digoxin during perioperative period.

4.2 Gastrointestinal drugs

As surgical trauma and other factors (mechanical ventilation, admission to ICU, etc.) can increase the risk of stress-induced mucosal injury, perioperative use of H₂ receptor blockers or proton pump inhibitors (PPI) to inhibit gastric acid production can reduce the occurrence of mucosal injury. The use of PPI is associated with the increased risk of *Clostridium difficile* infection. PPI H₂ receptor blockers have no obvious interaction with common narcotic drugs. It is recommended that patients with long-term use of H₂ receptor blockers or PPI should continue to use them during perioperative period. It is not recommended to use H₂ receptor blockers or PPI in all surgeries to prevent stress mucosal injury. Patients who can take these drugs orally should avoid intravenous use.

4.3 Respiratory drugs

4.3.1 Inhaled β receptor agonists and anticholinergics

In patients with chronic obstructive pulmonary disease and asthma, the use of β receptor agonists (salbutamol, salmeterol, formoterol) and anticholinergic drugs (ipratropium bromide, tiotropium bromide) can reduce the incidence of postoperative pulmonary complications. It is recommended that patients who use these drugs for a long time should continue to use them during perioperative period.

4.3.2 Theophylline

Excessive dose of theophylline may lead to severe arrhythmia and neurotoxicity, and metabolism of theophylline is affected by various drugs used during perioperative period. Therefore, it is recommended to stop taking theophylline before operation.

4.3.3 Glucocorticoids

Glucocorticoids are necessary to maintain optimal lung function. For patients who use glucocorticoids before surgery, the possibility of adverse reactions related to glucocorticoids (such as wound infection) during perioperative period is low. However, when faced with surgical stress, there is a risk of adrenal insufficiency. Therefore, it is recommended to continue the use of glucocorticoids during perioperative period.

4.3.4 Leukotriene inhibitors

Long-term use of leukotriene inhibitors (Zarukast and Montelukast) can be used to maintain the control of asthma symptoms, but they are not emergency treatment drugs. These drugs have a relatively short half-life, but they can control asthma symptoms and maintain lung function for 3 weeks after withdrawal. It is recommended to give leukotriene inhibitor in the morning of operation, and resume drug use when oral administration is tolerated after operation (only oral leukotriene inhibitor, no intravenous substitute).

4.4 Glucocorticoids

The indications of glucocorticoid use in perioperative period of ERAS include replacement therapy, prevention and treatment of postoperative nausea and vomiting, etc.

4.4.1 Alternative therapy

The alternative treatment plan should take into account the duration of glucocorticoid use and whether there is inhibition of hypothalamic-pituitary-adrenal axis (HPA), as well as the surgical mode and duration.

Patients without HPA inhibition, including those who have been treated with glucocorticoid for less than 3 weeks (dose not limited), those who take prednisone less than $5\text{mg}\cdot\text{d}^{-1}$ in the morning or other equivalent doses (duration not limited), and those who take prednisone of less than 10mg or other equivalent doses (duration not limited) every other day, are advised to continue to take the equivalent doses of glucocorticoid during perioperative period, and intravenous preparations can be used. Such patients do not need to increase the dose of glucocorticoids, nor do they need to evaluate the activity of HPA axis.

Patients with HPA axis inhibition, including prednisone dosage greater than $20\text{mg}\cdot\text{d}^{-1}$ for more than 3 weeks, or Cushing's syndrome, need to decide the dosage according to the type and duration of surgery. The recommended dose is as follows: low-risk operation or surgery with local anesthesia, using the original dose; For medium-risk surgery, the original dose should be used, and glucocorticoids should be supplemented: 50mg hydrocortisone should be given before operation, and then 25mg every 8 hours for 24 hours, after which the conventional dose can be restored; For high-risk surgery, the original dose should be used, and glucocorticoids should be supplemented: 100mg hydrocortisone should be given before surgery, then 50mg every 8 hours for 24 hours, and then the dose should be reduced by 50% every day until the dose used before surgery^[14, 15] or adjusted empirically according to clinical conditions. For other patients who cannot determine whether HPA axis inhibition occurs, it is recommended to evaluate the activity of HPA axis before operation, and comprehensively evaluate the dosage of glucocorticoid combined with medical history, medication history, operation type, anesthesia type and operation duration.

Patients with primary and secondary adrenocortical insufficiency can be treated empirically to prevent adrenocortical crisis. 25mg hydrocortisone can be given before low-risk surgery, 50mg during surgery, and the original oral dose can be restored after 1-2 days. 100-150mg hydrocortisone can be given before high-risk surgery, followed by 50mg hydrocortisone per hour and reduced daily by 50% to the preoperative dose after 2-3 days^[15].

4.4.2 Prevention and treatment of postoperative nausea and vomiting (PONV)

Dexamethasone takes a certain amount of time to take effect, and 8-10mg *iv* should be given before anesthesia induction. 2.5-5mg has proved to be effective, and the dose for children is $150\mu\text{g}\cdot\text{kg}^{-1}$. If PONV occurs after surgery, dexamethasone prophylactic therapy should not be used again for the failure, and the equivalent dose of methylprednisolone can be used^[15].

4.5 Diabetes drugs

Perioperative patients with hyperglycemia should be managed hierarchically to set different blood glucose

control targets. Perioperative blood glucose management should try to avoid hypoglycemia, large fluctuation of blood glucose, hyperglycemia and its associated infection risk. It is suggested that diabetic patients opt for morning surgery as much as possible to minimize the impact of fasting on blood glucose control. It is recommended that patients treated with oral hypoglycemic agents or non-insulin injectable formulations (GLP-1 analogues) discontinue the original regimen in the morning of surgery. Insulin is the first choice for blood glucose control during perioperative period. For non-critical patients underwent large and medium-sized surgery: Before operation, basic-meal insulin, subcutaneous injection of premixed insulin and subcutaneous injection of insulin pump can be adopted. During operation, subcutaneous injection of insulin should be stopped, and continuous intravenous infusion of insulin can be selected. After operation, insulin is continuously given to patients before they returned to a normal diet. After the patients' diet is restored, insulin should be changed to subcutaneous injection or transition to preoperative treatment. For patients who have good blood sugar control and can eat normally after minor surgery can continue the original treatment plan before surgery, and change it to half-dose medium-acting insulin or full-dose long-acting insulin analogue on the day of surgery. If stress hyperglycemia occurs during surgery, quick-acting insulin can be injected subcutaneously, and the original treatment plan will be restored after a normal diet after surgery. If the blood glucose control of patients is poor, it will be treated according to large and medium-sized surgery. Perioperative continuous intravenous insulin infusion is the first choice for critically ill patients. The dosage of insulin should be adjusted according to the fluctuation of blood glucose. After surgery, patients can change to subcutaneous insulin injection while eating a normal diet^[17-19].

Most hypoglycemic drugs can be continued according to the original treatment plan after patients return to a normal diet after surgery. However, in patients with suspected renal hypoperfusion, metformin needs to be resumed after clinical confirmation of normal renal function^[17, 20].

4.6 Antithrombotic drugs

Perioperative patients may increase the risk of venous thromboembolism (VTE) due to reduced preoperative activity, intraoperative immobilization, postoperative bed rest, anesthetic drugs and self factors including age, tumor and obesity. In addition, patients with a history of mechanical valve replacement, coronary stent implantation, atrial fibrillation, stroke, venous thromboembolism, etc. who have been using antithrombotic drugs for a long time while undergoing surgery should undergo preoperative evaluation, and perioperative antithrombotic drugs should be adjusted according to the evaluation results.

4.6.1 Perioperative VTE prevention in ERAS

Caprini model is recommended to evaluate VTE risk of patients, calculate the risk score and determine the risk grade of patients, dynamically evaluate the risk of thrombosis and bleeding, and choose the prevention methods. Heparin or low molecular weight heparin is the first choice for drug prevention. For patients with high risk of VTE but no risk of major bleeding, if they cannot tolerate heparin or low molecular weight heparin, such as those with a history of heparin-induced thrombocytopenia (HIT), fondaparinux sodium or aspirin can be considered for prevention. However, compared with low molecular weight heparin, fondaparinux sodium can increase the risk of major bleeding, so it is not recommended as a first-line medication. At present, there is no evidence for the use of novel oral anticoagulants to prevent VTE during perioperative period^[21-23].

4.6.2 Preoperative management of ERAS for patients undergoing and continued antithrombotic therapy

4.6.2.1 Antiplatelet drugs

It is recommended to conduct cardiovascular risk assessment, and assess the risk level of adverse cardiac reaction time within 30 days after surgery according to the type of operation^[22]. If necessary, preoperative assessment should be performed by MDT experts.

Patients who take aspirin alone can use aspirin without stopping because of their low risk of bleeding. For patients with low risk of cardiovascular events, aspirin should be stopped 7-10 days before surgery and recovered 24 hours after surgery. Those who are at high risk of cardiovascular events can keep taking the medicine and pay attention to the risk of bleeding. If the intraoperative hemodynamics is difficult to control, aspirin should be suspended before surgery. Aspirin will not interfere with the nerve block effect of

narcotic drugs, and has no effect on the duration of intraspinal catheter removal or postoperative detection^[24]. Those who take P2Y₁₂ receptor blockers, if they are not at risk of severe cardiovascular ischemia, may consider discontinuing tegrello or clopidogrel for 5 days or prasugrel for 7 days before operation. Preoperative discontinuation of ticagrelor or clopidogrel for 5 days or pragrael for 7 days may be considered in P2Y₁₂ receptor blockers without risk of severe cardiovascular ischemia.

Patients with a history of coronary stent placement who take dual antiplatelet drugs are treated with surgery for at least 6 weeks after metal bare stent placement or at least 6 months after drug-eluting stent placement, continue to use aspirin during the perioperative period, stop using ticagrelor or clopidogrel before surgery for 5 days, or stop using pragrael for 7 days, and recover 24 hours after surgery. In the case of surgery within 6 weeks after placement of a bare metal stent or 6 months after placement of a drug-eluting stent, it is recommended to continue with the original treatment before surgery. In case of severe bleeding, platelet or other hemostatic drugs can be injected. At present, there is no evidence of perioperative heparin bridging in patients on long-term antiplatelet medication^[24, 25].

Dipyridamole has vasodilating and antiplatelet effects. There is no data to support its safety for continuous use during perioperative period, and it is necessary to consider whether dipyridamole should be used continuously according to the risk of thrombosis and bleeding. If preoperative withdrawal is required, the use of dipyridamole should be stopped at least 2 days before surgery^[25].

4.6.2.2 Anticoagulant drugs

It is necessary to evaluate the bleeding risk according to the type of surgery to decide whether to stop anticoagulant drugs before operation. Anticoagulant therapy can be continued for patients with low bleeding risk, and it should be stopped before surgery for patients with moderate and high-risk bleeding risk. If the risk of thromboembolism increases, such as stroke and pulmonary embolism, it is recommended to postpone the operation until the risk drops to the previous basic level^[23, 24].

Long-term warfarin users should be evaluated for the risk of bleeding and thrombosis before surgery. Warfarin therapy should not be interrupted for low bleeding risk surgery, while it should be stopped before surgery for high risk surgery to further assess the risk of thrombosis. Medium to high risk of thromboembolism including mechanical mitral and aortic valve replacement, new stroke 12 weeks before surgery, systemic embolism, deep vein embolism, high risk of atrial fibrillation with stroke (CHADS₂ score of 5 to 6 points), recent stent placement, and history of thromboembolism during interruption of anticoagulant therapy, heparin or low molecular weight heparin bridging anticoagulant therapy is recommended, but novel oral anticoagulants are not recommended. When the risk of thromboembolism is low, including atrial fibrillation patients with CHADS₂≤4 and VTE patients, it is recommended that bridging anticoagulant therapy should not be performed, and International normalized ratio (INR) should be monitored within the treatment range. As the hemodynamics of the patients are stable after surgery, warfarin therapy should be resumed within 12-24 hours, and heparin drugs should be stopped when INR≥2.

Novel oral anticoagulants include direct thrombinase inhibitors (dabigatran etexilate) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). Perioperative discontinuation of anticoagulant therapy should also be determined according to the risk of surgical bleeding. Anticoagulant therapy should not be interrupted in low-bleeding risk surgery, while anticoagulant therapy should be stopped before high-risk surgery. Because of the short half-life of these drugs, heparin bridging anticoagulant therapy is not required.

4.7 Prevention and treatment drugs of PONV

The risk of PONV should be evaluated according to patient factors, anesthetic methods, selection of anesthetic drugs, operation duration and operation types. According to risk factors, the risk assessment of adult PONV can be conducted. Patients with low risk need not to take prophylactic medication, those with moderate risk can take one or two treatments for prevention, and those with high risk should take more than two treatments for prevention. The standard of clinical prevention and treatment effect of PONV is effective within 24 hours after surgery and no PONV at all. When prevention is ineffective, drugs with different mechanisms of action can be used^[26].

Treatment methods of PONV high-risk patients include non-drug methods: propofol anesthesia, local

anesthesia and acupuncture. The drug methods are as follows^[26].

4.7.1 Anticholinergic Drugs

Scopolamine patch in combination with other drugs is effective in treating PONV and studies have shown that scopolamine patch alone is equally effective in treating PONV as ondansetron or haloperidol monotherapy^[27].

4.7.2 Antihistamine drugs

The antiemetic effect of diphenhydramine $1\text{mg}\cdot\text{kg}^{-1}$ is similar to that of 5-HT₃ receptor antagonist, dexamethasone and droperidol, and there is a lack of research data on its combination with other drugs.

4.7.3 Glucocorticoids

The effect of dexamethasone 4-5mg after anesthesia induction is better than that after operation, which is similar to that of ondansetron 4mg or haloperidol 1.25mg. Some studies have reported that the effect of dexamethasone 8mg is better than that of 4-5mg. Most reports indicate that a single dose of dexamethasone during perioperative period does not increase the risk of wound infection. In addition, dexamethasone has increased the risk of blood glucose, so the advantages and disadvantages should be weighed when it is used in obese patients and diabetic patients^[28].

4.7.4 5-HT₃ receptor antagonists

Drugs including ondansetron, tropisetron, and palonosetron can be given after surgery. For the prevention of PONV, multiple administrations of these drugs are not recommended. If the effect is not good, another kind of drug can be used. There are no differences in efficacy and safety among the different drugs.

4.7.5 Phenothiazines

The dosage of perphenazine for preventing PONV is 2.5-5mg; Metoclopramide has a limited effect in treating PONV, and a dose of 10mg cannot effectively reduce the risk of PONV. Only when it is greater than 20mg can it have anti-vomiting effect. The preventive effect of metoclopramide 25-50mg for advanced PONV is similar to that of ondansetron 4mg^[29].

4.7.6 NK-1 receptor antagonists

24-48 hours after surgery, aprepitant is better than ondansetron in preventing PONV, and aripipran 40mg combined with dexamethasone is better than that of ondansetron combined with dexamethasone in preventing PONV^[30], but the drugs are not used as routine prevention of PONV due to relatively few clinical study data.

4.7.7 Butyrophenones

Butyrophenones are not the first-line prophylactic drugs for PONV. Low-dose droperidol of 0.625-1.25mg can effectively prevent PONV, and the effect is similar to that of ondansetron 4mg. Droperidol can lead to prolonged QT interval and tip torsion-induced ventricular tachycardia, but this adverse reaction is time- and dose-dependent, so it is very unlikely that low-dose droperidol can induce this cardiovascular time. Studies have shown that the combination of droperidol and ondansetron can effectively prevent PONV, with no difference in the QT interval compared with placebo and ondansetron monotherapy^[31]. Haloperidol is a substitute for droperidol, and there is no difference between the efficacy of haloperidol 1mg and droperidol 0.625mg after anesthesia induction in preventing PONV.

4.7.8 Anaesthetics

Midazolam can reduce the incidence of PONV. The effect of midazolam 2mg and ondansetron 4mg 30 min before the end of the operation is similar. There is no difference between midazolam $0.075\text{mg}\cdot\text{kg}^{-1}$ and dexamethasone 10mg in preventing PONV.

For PONV occurred within 6 hours after surgery: In patients who failed prophylactic therapy with 5-HT₃ receptor antagonist, dexamethasone, haloperidol or haloperidol at the beginning, these 3 drugs should not be reused within 6 hours, and other drugs should be selected. For PONV occurred after 6 hours after surgery: Except dexamethasone and M-receptor blocker (scopolamine), other preventive drugs could be used repeatedly with the same dosage as before; When the initial scheme is HT₃ receptor antagonist plus another drug, different kinds of 5-HT₃ receptor antagonist and two other drugs can be selected^[26].

4.8 Postoperative analgesic drugs

The postoperative pain includes inflammation caused by tissue trauma or direct nerve injury. The following factors should be considered for postoperative analgesia: age, anxiety, surgical methods and procedures, individual physical condition, response to medication or treatment, etc. The best way of perioperative analgesia in ERAS is to take multi-mode analgesia to reduce the postoperative demand for opioids^[32-34].

Commonly used analgesic drugs include:

(1) Opioids

Narcotic analgesics are divided into weak and strong opioids according to their analgesic intensity. Weak opioids include codeine, dihydrocodeine, etc., which are used to relieve mild to moderate acute pain. Strong opioids include morphine, fentanyl, meperidine, sufentanil, oxycodone, hydromorphone, etc., which are mainly used to treat moderate to severe postoperative pain. The agonist-antagonist butorphanol, desoxacin, pentazoxin and partial agonist buprenorphine can be used as multimodal analgesia for the treatment of severe pain.

The analgesic effects and adverse reactions of opioids are dose-dependent and receptor-dependent, without organ toxicity or capping effect. The application of opioids should follow the principle of maximum analgesia and no intolerable adverse reactions, and multi-mode analgesia should be advocated. The adverse reactions of opioids can be treated by discontinuing or reducing the dosage of opioids, symptomatic treatment of adverse reactions, switching to other types of opioids and changing the administration route.

(2) NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) can be divided into non-selective NSAIDs and selective COX-2 inhibitors, which can be used for postoperative analgesia of mild to moderate pain or multimodal analgesia of moderate to severe pain. The analgesic effect of NSAIDs has a ceiling effect, which is different from that of opioids, that is, the effect does not increase with the increase of drug dose after the analgesic effect reaches a certain level, so it is not recommended to use NSAIDs in over dose, and the combination of two kinds of NSAIDs should be avoided. The analgesic effect of NSAIDs after surgery may be equivalent to that of low dose morphine or oxycodone^[35, 36]. A large number of long-term non-selective NSAIDs and selective COX-2 inhibitors can cause adverse reactions, including renal function damage and increased cardiovascular risk, which are related to the dosage and time of use, and whether there are any risk factors for the use of COX inhibitors. Patients with risk factors should carefully considered in choosing these drugs, and intravenous drug use generally does not last exceed 3-5 days.

Oral drugs of non-selective NSAIDs include ibuprofen, diclofenac, meloxicam and lornoxicam, while the injection drugs include lornoxicam, ketorolac and flurbiprofen axetil. The preventive analgesic effects of non-selective NSAIDs are still controversial, thus it is necessary to evaluate the risk factors when using them. Non-selective NSAIDs have great gastrointestinal adverse reactions, which are more likely to occur, especially in patients with a history of taking anticoagulants, glucocorticoids, aspirin or digestive tract ulcers. Therefore, H2 receptor blockers, PPI, etc. or selective COX-2 inhibitors should be added when necessary^[37, 38].

Selective COX-2 inhibitors have a long half-life, which can directly inhibit the sensitization of the pain center and increase the pain threshold through the blood-brain barrier, and can be used for preventive analgesia^[38]. Compared with non-selective NSAIDs, they can reduce the gastrointestinal adverse reactions caused by the inhibition of COX-1.

(3) Tramadol

Non-opioid central analgesics can be used for moderate and severe pain and postoperative analgesia. Tramadol with equivalent dose has the same effect as pethidine, and can be combined with acetaminophen and NSAIDs. Compared with opioids, tramadol has a relatively small risk of respiratory depression and gastrointestinal function inhibition.

(4) Local anesthetics

Postoperative analgesia can be performed by surface anesthesia, infiltration anesthesia, nerve block and

other methods. Combined use with opioids can enhance the analgesic effect and prolong the analgesic time.

4.9 Muscle relaxants

According to the expert consensus of perioperative management of enhanced recovery after surgery in China, intraoperative muscle relaxation monitoring is recommended to evaluate the degree of neuromuscular block, so as to avoid insufficient or excessive use of muscle relaxants. Currently, the most effective muscle relaxants are succinylcholine and rocuronium bromide. To reduce residual muscle relaxation after surgery, the commonly used drugs cholinesterase inhibitors and the specific antagonist of novel amino steroidal muscle relaxant sugammadex sodium can be used.

4.10 Enteral and parenteral nutrition preparations

All patients need to undergo nutritional risk screening (NRS-2002) and nutritional assessment before surgery. The contents of NRS-2002 include BMI<20.5 kg·m⁻², weight loss>5% within 3 months, inability to eat, and disease severity^[39]. NRS-2002 can be used as a risk screening tool. Nutritional assessment methods include weight loss, body mass index, fat-free body mass index, nutritional risk index, subjective comprehensive assessment methods, etc., and serum protein can be used as auxiliary evaluation indicators^[39, 40].

Oral nutrition supplement (ONS) or enteral nutrition (EN) is the first choice for perioperative nutritional support in ERAS. When EN cannot be implemented or EN cannot provide sufficient energy and protein, parenteral nutrition (PN) should be supplemented or selected. Among them, the use of ONS in the perioperative period is the most important nutritional treatment in ERAS. For patients with obvious malnutrition, ONS is given as preoperative nutritional treatment, and early postoperative feeding or ONS can protect the intestinal mucosa and promote the recovery of intestinal function, and reduce the occurrence of systemic infection and insulin resistance^[40, 41].

The main evaluation parameters of enteral nutrition preparations include energy density, protein content, protein source (amino acid mixture, hydrolyzed protein, and whole protein) and feeding route, while the secondary evaluation indicators include osmotic pressure, fat content, fat source, dietary fiber content, lactose content, electrolyte, mineral and vitamin content, dosage form and price^[42]. The most common complications of ONS and EN are gastrointestinal complications, which are manifested as abdominal distension, diarrhea, nausea, vomiting, intestinal spasm, etc. When it occurs, it is necessary to determine whether there is mechanical or paralytic intestinal obstruction, whether it is related to the type of preparation, and whether it is related to other treatment and medication of the patient, and then relevant symptoms and causes are treated or ONS or EN are stopped. Parenteral nutrition formula includes water, glucose, amino acids, fat emulsion, electrolytes, various trace elements and vitamins. In addition, glutamine, ω-3 fatty acids can also be added to the suspension, and the addition, adding order, and adding method may affect its stability and compatibility^[43].

Attached table:

Category	List of drugs to be focused on during perioperative period
Cardiovascular drugs	β receptor blockers; Calcium channel blockers; RASS inhibitors (ACEI and ARB); Diuretics; Lipid-lowering drugs; Digoxin
Gastrointestinal drugs	Proton pump inhibitors (PPI); H2 receptor blockers
Respiratory drugs	Inhaled β receptor agonists and anticholinergics; Theophylline; Glucocorticoids; Leukotriene inhibitors
Glucocorticoids	Hydrocortisone, Prednisone, Methylprednisolone, Dexamethasone
Diabetes drugs	Insulin; Sulfonylureas; Biguanides; α-glycosidase inhibitors; Thiazolidinediones
Antithrombotic drugs	Low molecular weight heparin/heparin; Antiplatelet drugs; Anticoagulant: Warfarin, Novel oral anticoagulants
Prevention and treatment drugs of nausea and vomiting	Anticholinergic drugs; Antihistamine drugs; Glucocorticoids; 5-HT3 receptor antagonists; Phenothiazines; NK-1 receptor antagonists; Butyrophenones; Anaesthetics
Postoperative analgesic drugs	Opioids; NSAIDs: non-selective and selective COX-2 inhibitors; Tramadol; Local anesthetics
Muscle relaxants	cholinesterase inhibitors; specific antagonist of novel amino steroidal

	muscle relaxant
Enteral and parenteral nutrition preparations	Oral nutritional supplements (ONS) or enteral nutrition (EN); Parenteral nutrition

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References

- [1] McIsaac DI, Wong CA, Bryson GL, et al. Association of Polypharmacy with Survival, Complications, and Healthcare Resource Use after Elective Noncardiac Surgery: A Population-based Cohort Study. *Anesthesiology* 2018;128:1140-1150.
- [2] Wallace AW, Au S, Cason BA. Association of the pattern of use of perioperative beta-blockade and postoperative mortality. *Anesthesiology* 2010;113:794-805.
- [3] Friedell ML, Van Way CW, 3rd, Freyberg RW, et al. β -Blockade and Operative Mortality in Noncardiac Surgery: Harmful or Helpful? *JAMA Surg* 2015;150:658-63.
- [4] Finegan BA, Hussain MD, Tam YK. Pharmacokinetics of diltiazem in patients undergoing coronary artery bypass grafting. *Ther Drug Monit* 1992;14:485-92.
- [5] Wijeyesundera DN, Beattie WS, Rao V, et al. Calcium antagonists are associated with reduced mortality after cardiac surgery: a propensity analysis. *J Thorac Cardiovasc Surg* 2004;127:755-62.
- [6] Wijeyesundera DN, Beattie WS. Calcium channel blockers for reducing cardiac morbidity after noncardiac surgery: a meta-analysis. *Anesth Analg* 2003;97:634-641.
- [7] Lonjaret L, Lairez O, Minville V, et al. Optimal perioperative management of arterial blood pressure. *Integr Blood Press Control* 2014;7:49-59.

- [8] Lee SM, Takemoto S, Wallace AW. Association between Withholding Angiotensin Receptor Blockers in the Early Postoperative Period and 30-day Mortality: A Cohort Study of the Veterans Affairs Healthcare System. *Anesthesiology* 2015;123:288-306.
- [9] Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J* 2014;35:2383-431.
- [10] Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. *Can J Cardiol* 2017;33:17-32.
- [11] Khan NA, Campbell NR, Frost SD, et al. Risk of intraoperative hypotension with loop diuretics: a randomized controlled trial. *Am J Med* 2010;123:1059 e1-8.
- [12] Auerbach A, Goldman L. Assessing and reducing the cardiac risk of noncardiac surgery. *Circulation* 2006;113:1361-76.
- [13] Amend KL, Landon J, Thyagarajan V, et al. Incidence of hospitalized rhabdomyolysis with statin and fibrate use in an insured US population. *Ann Pharmacother* 2011;45:1230-9.
- [14] Endert E, Ouweland A, Fliers E, et al. Establishment of reference values for endocrine tests. Part IV: Adrenal insufficiency. *Neth J Med* 2005;63:435-43.
- [15] Xu JG, Tang H, Yao SL, et al. Expert consensus on perioperative administered glucocorticoids in clinic application. *Journal of Clinical Anesthesiology* 2017; 33:712-716.
- [16] Buchleitner AM, Martinez-Alonso M, Hernandez M, et al. Perioperative glycaemic control for diabetic patients undergoing surgery. *Cochrane Database Syst Rev* 2012:CD007315.
- [17] Dhataria K, Levy N, Kilvert A, et al. NHS Diabetes guideline for the perioperative management of the adult patient with diabetes. *Diabet Med* 2012;29:420-33.
- [18] Gao H. Expert consensus on perioperative blood glucose management (Ahead of print). *Journal of Clinical Anesthesiology* 2016;32:93-95.
- [19] Guangdong Pharmaceutical Association. Expert consensus on the perioperative blood glucose management. *Pharmacy Today* 2018;28:73-83.
- [20] Canadian Diabetes Association Clinical Practice Guidelines Expert C, Booth G, Cheng AY. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. *Methods. Can J Diabetes* 2013;37 Suppl 1:S4-7.
- [21] Hornor MA, Duane TM, Ehlers AP, et al. American College of Surgeons' Guidelines for the Perioperative Management of Antithrombotic Medication. *J Am Coll Surg* 2018;227:521-536 e1.
- [22] Liu FL, Zhang TP. Guidelines for prevention and management of perioperative venous thrombosis in general surgery in China. *Chinese Journal of Practical Surgery* 2016;36:469-474.
- [23] Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur J Anaesthesiol* 2014;31:517-73.
- [24] Narouze S, Benzon HT, Provenzano D, et al. *Interventional Spine and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications (Second Edition): Guidelines From the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain.* *Reg Anesth Pain Med* 2018;43:225-262.
- [25] Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;143:1-13.
- [26] Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2014;118:85-113.
- [27] White PF, Tang J, Song D, et al. Transdermal scopolamine: an alternative to ondansetron and droperidol for the prevention of postoperative and postdischarge emetic symptoms. *Anesth Analg* 2007;104:92-6.
- [28] Collaborators DT, West Midlands Research C. Dexamethasone versus standard treatment for postoperative nausea and vomiting in gastrointestinal surgery: randomised controlled trial (DREAMS Trial). *BMJ* 2017;357:j1455.
- [29] Isazadehfar K, Entezariasl M, Shahbazzadegan B, et al. The Comparative Study of Ondansetron and Metoclopramide Effects in Reducing Nausea and Vomiting After Laparoscopic

- Cholecystectomy. *Acta Med Iran* 2017;55:254-258.
- [30] Habib AS, Keifer JC, Borel CO, et al. A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy. *Anesth Analg* 2011;112:813-8.
- [31] Chan MT, Choi KC, Gin T, et al. The additive interactions between ondansetron and droperidol for preventing postoperative nausea and vomiting. *Anesth Analg* 2006;103:1155-62.
- [32] Expert consensus on perioperative administration of non-steroidal anti-inflammatory drugs for enhanced recovery after surgery in China. *Chinese Journal of General Surgery* 2019;3:283-288.
- [33] Leng XS, Wei JM, Liu LX, et al. Expert consensus on perioperative pain treatment in general surgery. *Chinese Journal of General Surgery* 2015;30:166-173.
- [34] Wang GL, Cang J, Deng XM, et al. Expert consensus on perioperative application of non-opioid analgesics in adults. *International Journal of Anesthesiology and Resuscitation* 2019;1:1-6.
- [35] Oscier CD, Milner QJ. Peri-operative use of paracetamol. *Anaesthesia* 2009;64:65-72.
- [36] Malan TP, Jr., Gordon S, Hubbard R, et al. The cyclooxygenase-2-specific inhibitor parecoxib sodium is as effective as 12 mg of morphine administered intramuscularly for treating pain after gynecologic laparotomy surgery. *Anesth Analg* 2005;100:454-460.
- [37] Su C, Su Y, Chou CW, et al. Intravenous flurbiprofen for post-thymectomy pain relief in patients with myasthenia gravis. *J Cardiothorac Surg* 2012;7:98.
- [38] Ong CK, Lirk P, Tan CH, et al. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin Med Res* 2007;5:19-34.
- [39] Wischmeyer PE, Carli F, Evans DC, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Nutrition Screening and Therapy Within a Surgical Enhanced Recovery Pathway. *Anesth Analg* 2018;126:1883-1895.
- [40] Weimann A, Braga M, Carli F, et al. ESPEN guideline: Clinical nutrition in surgery. *Clin Nutr* 2017;36:623-650.
- [41] Chinese Society for Parenteral and Enteral Nutrition. Guidelines on perioperative nutrition support for adults. *Chinese Journal of Surgery* 2016;54:641-657.
- [42] Guangdong Pharmaceutical Association. Clinical Pharmacy consens on enteral nutrition (version 2.0). *Pharmacy Today* 2017;27:361-371.
- [43] Guangdong Pharmaceutical Association. Clinical Pharmacy consens on parenteral nutrition (version 2.0). *Pharmacy Today* 2017;27:289-303.