

# The use of nalbuphine in paediatric anaesthesia

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## Abstract

Nalbuphine is an agonist-antagonist opioid that has analgesic and sedative effects, and because of the ceiling effect, it does not cause respiratory depression. In the perioperative therapy of paediatric patients, it can be used for premedication, sedation during diagnostic procedures, and postoperative pain treatment. Nalbuphine reverses the adverse reactions of other opioids (e.g., itching, urine retention) without significantly influencing its analgesic properties. Following sevoflurane anaesthesia in small children, it reduces the incidences of agitation. Nalbuphine is considered to be a safe drug and one that causes fewer instances of nausea and vomiting compared with other opioids. Its analgesic effect, combined with its ability to provide moderate sedation with a large margin of safety, makes it the most frequently used analgesic in paediatric patients.

**Key words:** postoperative analgesia, nalbuphine, children

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Nalbuphine is a synthetic opioid agonist-antagonist analgesic derivative of the phenanthrene group, and its structure is similar to those of naloxone and oxymorphone. The drug is used for managing slight and moderate pain. It acts as an agonist of kappa opioid receptors (KORs) and mu opioid receptors (MORs), thus providing analgesia as well as sedation, and it protects against receptor blockade-dependent respiratory failure. Nalbuphine exhibits a ceiling effect; in other words, once its maximum plasma concentration has been reached, incremental doses do not potentiate its analgesic effects or increase the risk of respiratory failure [1]. Therefore, nalbuphine is considered a drug with a relatively slight risk of inducing respiratory failure. Because nalbuphine's specific mechanism of action provides potent analgesic effects, moderate sedation and relatively rare adverse side effects, and the drug is readily used for pain management in children.

Nalbuphine can be administered parenterally but is poorly absorbed from the gastrointestinal tract. Its therapeutic plasma concentration to provide effective analgesia is  $12 \mu\text{g L}^{-1}$ . It is metabolised in the liver by cytochrome P-450, CYP 3A4 and 2C19 and broken down into N-hydroxy-ceto-cyclo-butyl-methyl-nornalbuphine, and hydroxylated derivatives are excreted through the kidneys. The mechanism of hepatic clearance is strictly correlated with the extent of

blood flow through the liver and is age dependent. Hepatic clearance is low during the neonatal period and increases with age, reaching its maximum at approximately 1 year of age and thereafter decreases gradually until adulthood [2]. Its elimination half-life ranges from 0.9 h in children aged 1.5–8.5 years to 1.9 h in young adults [3].

Nalbuphine-induced analgesia and sedation as well as the ability to cause dysphoria result from the activation of KORs, whereas its antagonistic effects against MORs reduce the risk of respiratory depression caused by the agonist opioids that are used during surgical procedures. Moreover, because of its ceiling effect, nalbuphine protects against respiratory depression during treatment. The dose of maximum analgesic action is  $0.3\text{--}0.4 \text{ mg kg}^{-1}$ . Higher doses neither increase the analgesic effects nor substantially increase the risk of respiratory failure. A neonate mistakenly administered a dose ten-fold higher than required has been described and resulted in only a prolonged sedation without respiratory failure [4]. The drug used in recommended doses is believed not to induce respiratory depression in children. Many authors consider that the profile of its action is safe [4–6]. Nevertheless, caution should be exercised in patients with an increased risk of respiratory failure, including children with neuromuscular diseases or impaired regulation of the respiratory centre, following cerebrocranial injuries, or in patients who are con-

currently receiving other drugs that are likely to induce respiratory depression. In such patients, dosing of nalbuphine should be cautious and meticulously titrated; moreover, basic vital functions should be continuously monitored.

The other adverse effects of nalbuphine, although relatively rare, include drowsiness, vomiting, dysphoria and skin redness. According to Bressole et al., drowsiness is observed in 32% of patients, whereas 13.6% experience vomiting or urine retention after receiving nalbuphine following laparoscopic fundoplication for gastroesophageal reflux [2]. Nalbuphine exerts slight effects on gastrointestinal peristalsis. Compared with other opioids, the nalbuphine-induced incidence of nausea and vomiting is lower [4]. Moreover, nalbuphine does not affect the detrusor urinae muscle and, thus, should not cause bladder voiding-associated problems. High bolus doses can induce dysphoric disorders, especially in older children. To avoid such disturbances, the drug should be titrated, and a single dose should not exceed 5 mg [4]. Nalbuphine has no addictive potential; however, it should be noted that in patients who are addicted to opioids, its antagonistic effects on MORs could cause withdrawal syndrome symptoms. Compared with morphine, nalbuphine exhibits weaker analgesic effects, and its dose cannot be freely escalated due to the ceiling effect mentioned above; however, it poses a substantially lower risk of adverse side effects (respiratory depression, nausea and vomiting, pruritus or urine retention). Moreover, its influence on the cardiovascular system is weaker than that of morphine [2]. Compared with tramadol, morphine shows comparable analgesic effects and induces stronger and longer sedation. Its administration is less commonly associated with nausea and vomiting; in addition, the stability of analgesia is found to be higher when administered via continuous intravenous infusions [8–10].

Nalbuphine has been used for many years for pain management in adults as well as children. In Poland, it has been available since 2013 and has been approved for pain therapy in patients above the age of 18 months. It is not included on the list of intoxicating narcotic agents and psychotropic substances and can thus be stored with other non-intoxicating narcotic drugs and ordered on a routine basis.

### **NALBUPHINE FOR POSTOPERATIVE PAIN MANAGEMENT IN CHILDREN**

Surgery is extremely stressful for any child, and the pain associated with tissue damage is an adverse experience. The perception of pain by children during the postoperative period has been demonstrated to be associated with an increased incidence of perioperative complications, longer hospitalisations and slower wound healing. If poorly treated, pain can cause changes in the pain perception threshold or emotional disorders in later life. Perioperative management

of young children should also consider the specificity of their mentality and the degree of development; an inability to understand the situation and reluctance to cooperate may influence the perioperative pain management of children. To provide children with maximum comfort during and after surgical procedures, new methods for effective and safe postoperative analgesia are being pursued. Currently, pain is managed by using all available methods concurrently: regional (ranging from injections into the surgical wounds, to various regional anaesthesia techniques, to continuous block anaesthesia); pharmacological anaesthesia using the synergistic effects of analgesics with various mechanisms of action and supportive preparations of sedative, anti-anxiety, antiemetic and hypnotic effects as well as non-pharmacological analgesia, including all measures aimed at providing children with a friendly and empathic atmosphere; and finally, accessibility to various activities and games that can distract them. The continuous presence of parents is essential because the company of relatives calms children, improves their comfort and reduces their analgesic requirements [11, 12].

Considering its ability to induce moderate sedation and potent analgesic effects, nalbuphine is one of the drugs that is recommended for postoperative pain management in children above the age of 18 months [3]. It is suitable for pain management following surgical procedures causing moderate to strong complaints, both in monotherapy and in combination with non-opioid analgesics or regional analgesia. However, it is not sufficiently potent as a monotherapy after more extensive procedures such as thoracotomy or extensive abdominal or orthopaedic surgery.

Nalbuphine can be administered intravenously, intramuscularly, subcutaneously or intrathecally. The enteral route of administration should be avoided due to uncertain and changeable absorption from the gastrointestinal tract. A single intravenous dose begins to act within 2–3 minutes and reaches its maximum analgesic effect after approximately 10 minutes; its analgesic effects are maintained for 120–300 minutes. Intramuscular nalbuphine should not be used in children due to additional pain sensations and uncertain absorption from the muscles, which lead to difficulties in assessing its analgesic effects.

Nalbuphine for postoperative pain management can be used in boluses at a dose of 0.2 mg kg<sup>-1</sup>, repeated every 3–6 h as needed. If the repeated boluses are insufficient or a child requires too frequent a supply of further doses, a continuous intravenous infusion at a dose of 0.1 mg kg<sup>-1</sup> h<sup>-1</sup> should be contemplated, which provides stable and effective postoperative analgesia. In patients undergoing procedures with more extensive tissue damage, patients requiring forced immobilisation after surgery, and patients in whom moderate sedation can be beneficial for the postoperative

**Table 1.** Dosage of nalbuphine for postoperative pain management in children

Bolus dose	0.2 mg kg <sup>-1</sup>	Repeated every 3–6 h
Continuous infusion	0.1–0.2 mg kg <sup>-1</sup> h <sup>-1</sup>	Continuous intravenous infusion
PCA	Basal infusion 0.02 mg kg <sup>-1</sup> h <sup>-1</sup> Bolus — 0.02 mg kg <sup>-1</sup> Intervals between boluses 5 min. Max. dose within 2 h 0.4 mg kg <sup>-1</sup>	

period, nalbuphine should be administered in a continuous intravenous infusion in a dose of 0.1 mg kg<sup>-1</sup> h<sup>-1</sup> immediately after surgery. In cases of insufficient analgesia, the rate of infusion can be increased up to 0.2 mg kg<sup>-1</sup> h<sup>-1</sup> [4].

Moreover, nalbuphine can be administered by patient-controlled analgesia (PCA) [14]. This method ensures stable analgesia, and the potential applications of the drug in cases of increased pain are well understood and accepted in older children. The basic PCA dosing includes a basal infusion in a dose of 0.02 mg kg<sup>-1</sup> h<sup>-1</sup> and a bolus dose of 0.02 mg kg<sup>-1</sup>; the interval between successive boluses is 5 min. The max dose during a 2-hour period should not exceed 0.4 mg kg<sup>-1</sup> [4]. The nalbuphine dosage for postoperative pain management in children is presented in Table 1.

During the use of nalbuphine for postoperative pain management, its ceiling effect should be considered. Failed pain reduction despite the administration of a maximum dose combined with non-opioid analgesics or regional analgesia, is likely to indicate that the maximum pain relief has been achieved and that a change of opioid is required. The inclusion of a pure MOR opioid agonist after therapy with the drug of agonistic-antagonistic action is generally associated with the necessity to apply a higher dose to expel the antagonist from the receptor site. Therefore, the initial dose should be carefully titrated until the satisfactory analgesic effect is achieved.

#### OTHER APPLICATIONS OF NALBUPHINE

All anaesthesiologists who provide paediatric anaesthesia are faced with the issue of the postoperative excitation of children following sevoflurane anaesthesia. This issue predominantly concerns pre-school children; its cause has not been fully elucidated, but post-sevoflurane excitation is estimated to occur in over 30% of children undergoing general anaesthesia with sevoflurane for non-surgical procedures [15, 16]. The incidence of excitation following anaesthesia can be reduced by using propofol, ketamine or nalbuphine during the final stage of anaesthesia [15, 17, 18]. Nalbuphine in a dose of 0.1 mg kg<sup>-1</sup> administered at the end of anaesthesia has been shown to decrease the incidence

of excitation and anxiety after anaesthesia more effectively than ketamine without prolonging the awakening time [18].

Sedative and tranquillising effects are extremely beneficial in emergency cases. In an injured, anxious and suffering child, a single nalbuphine dose of 0.1–0.2 mg kg<sup>-1</sup> reduces the severity of pain and induces tranquillity. However, caution should be exercised in haemodynamically unstable children or in those with craniocerebral injuries because such patients are especially at risk of respiratory failure. In such cases, the titration of the analgesic doses and the continuous monitoring of basic vital signs are recommended. Analgesic and sedative action can be used in premedication of patients with preoperative pain (injuries, fractures, emergency conditions). The use of nalbuphine at a dose of 0.1–0.2 mg kg<sup>-1</sup> for premedication ensures pain reduction, sedation and tranquillity.

Because of its agonistic-antagonistic mechanism of action, nalbuphine can be additionally applied to prevent the adverse side effects induced by other opioids without neutralising their analgesic effects. Some promising reports have revealed that nalbuphine, in addition to naloxone, naltrexone and droperidol, is effective for the prevention and treatment of pruritus caused by intravenous or intrathecal opioids [19, 20]; however, some authors have not confirmed its efficacy for pruritus treatment [21]. Nalbuphine alleviates other adverse effects of opioids, including reversing the urine retention caused by intravenous or epidural morphine, without eliminating its analgesic effects [22, 23] or reversing the respiratory depression caused by opioids [24–27]. Unfortunately, the available data are insufficient to appropriately assess nalbuphine's impact on opioid-induced gastrointestinal dysfunction [28].

Nalbuphine is a drug that can be used during general anaesthesia for low-pain surgical procedures [29–31] and for maintaining sedation during or after surgery in patients undergoing block anaesthesia [32–34]. Many authors have reported its efficacy for sedation during painless diagnostic procedures associated with forced long-term immobilisation, such as computed tomography or magnetic resonance imaging. The use of sedation with nalbuphine in a dose of 0.1 mg kg<sup>-1</sup> combined with midazolam (0.1 mg kg<sup>-1</sup>) and

a continuous infusion of propofol (5 mg kg<sup>-1</sup> h<sup>-1</sup>) enables safe MRI examinations [35, 36].

Furthermore, nalbuphine is effective for the treatment of pain unrelated to surgery or trauma. Because of its safety profile, nalbuphine can be used for pain management in children with burns [37], neoplastic or haematological diseases. It is effective in pain episodes in patients with sickle cell anaemia. Lower incidence rates of acute chest syndrome (ACS) episodes have been described in patients and sickle cell disease whose pain was treated with nalbuphine compared with other opioids [38–40].

The number of reports regarding the use of nalbuphine in children under the age of 18 months are limited; those that are available, however, describe its effective and safe use in infants and newborns during the perioperative period and as sedation for painful procedures or mechanical ventilation in neonatal intensive care units [30, 41–43].

## SUMMARY

Nalbuphine is an agonistic-antagonistic opioid that produces moderate sedative and medium analgesic effects. It provides satisfactory analgesia after minor, medium and extensive procedures. The drug shows a beneficial additive effect with non-opioid analgesics and regional analgesia. Based on its efficient analgesia and moderate sedation, nalbuphine induces its effects as well as a beneficial safety profile for use in the postoperative pain management of children. It can be used during the perioperative period for premedication, sedation for minor surgical procedures and diagnostic examinations. Its analgesic and sedative effects can be used in emergency medicine and to treat neoplastic pain. Nalbuphine possesses a wide safety margin, and its recommended doses do not induce respiratory failure. Compared with other opioids, nalbuphine results in fewer incidences of nausea and vomiting and can even prevent the adverse side effects incurred by other opioids. The drug in question excellently supplements the list of analgesics that can be applied for paediatric pain management.

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