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## An extensive review of Nalbuphine's hemodynamic effects in ear, nose, and throat (ENT) surgeries

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### Abstract

The semi-synthetic opioid nalbuphine has drawn interest due to its analgesic qualities; however, further research is needed to determine how it specifically affects hemodynamics during ear, nose, and throat (ENT) procedures. In order to comprehend the complex hemodynamic effects of nalbuphine during ENT procedures, this thorough review attempts to methodically analyse the body of literature currently in publication. During ENT procedures, nalbuphine shows potential as an analgesic medication with typically stable hemodynamic characteristics. However, a cautious interpretation is required due to the heterogeneity in study designs and outcomes. The study emphasises the necessity of standardising procedures and doing additional research to clarify patient-specific factors and guarantee the best possible use of nalbuphine in improving ENT patients' overall perioperative care.

**Keywords:** Nalbuphine, kappa receptors, hemodynamic effects, FES surgeries

### Introduction

Because of its unique pharmacological profile, nalbuphine, a semi-synthetic mixed agonist/antagonist opioid modulator belonging to the phenanthrene or morphinan class, has gained interest in perioperative treatment<sup>[1]</sup>. Nalbuphine was first prescribed as an analgesic in the late 1970s. However, it has a complex interaction with opioid receptors, functioning as both an antagonist on mu receptors and an agonist on kappa receptors. It differs from traditional opioids due to its distinct dual action, which makes it an interesting and distinctive option for pain management<sup>[2]</sup>.

From simple tonsillectomies to complex rhinoplasties and functional endoscopic sinus (FES) surgeries, the field of ear, nose and throat (ENT) surgery presents special challenges<sup>[3-5]</sup>. It is frequently crucial to have regulated hypotension, especially in these situations. In order to maximise surgical visibility and reduce blood loss, controlled hypotension entails purposefully lowering blood pressure. This requires a careful balancing act on cardiovascular factors. Vigilant management over blood pressure and heart rate is crucial to minimise problems and improve patient outcomes because of the close proximity of key structures, complex vascular anatomy, and possibility for bleeding<sup>[4]</sup>. Notably, many procedures may explicitly require hypotensive anaesthesia, including regular tonsillectomies, rhinoplasties, and FES surgeries<sup>[3-5]</sup>.

This thorough review's main goal is to examine and compile the body of research on nalbuphine's hemodynamic effects, particularly as it relates to ENT procedures. This review seeks to clarify the impact of nalbuphine on important cardiovascular parameters by exploring its pharmacology and distinct receptor interactions. Furthermore, we will assess clinical research and data rigorously in order to provide insight into the safety record, side effects, and possible advantages of nalbuphine in relation to ENT surgical procedures. With the use of this synthesis, we intend to shed light on nalbuphine's function in maximising hemodynamic stability during ENT procedures and open up new study directions for researchers and clinicians.

### Hemodynamic stability in ENT surgeries

**Controlled hypotension:** Induced hypotension is used in ENT surgeries to enhance surgical visibility and minimize blood loss. However, it is imperative to uphold hemodynamic stability throughout the intraoperative period.

A study that compared the utilization of dexmedetomidine and esmolol revealed that dexmedetomidine, functioning as an alpha-2 adrenergic agonist, exhibited superior efficacy in maintaining hemodynamic stability, particularly noted during FES surgery [5].

### Preventing hemodynamic instability

A number of factors, such as components inherent to the surgical process, factors particular to the patient, and factors connected to anaesthesia, can affect the incidence of postoperative hemodynamic instability [6]. The mitigation of hemodynamic instability and the enhancement of overall patient outcomes heavily depend on the early identification and aggressive management of these risk factors.

Keeping an eye on hemodynamic parameters During ENT procedures, careful monitoring of hemodynamic parameters such blood pressure, heart rate, and oxygen saturation is essential. In addition to ensuring patient safety, this close supervision makes it easier to identify any changes in hemodynamic condition early on [5]. Such careful observation is essential for prompt interventions and greatly enhances the general safety and effectiveness of ENT treatments.

### Nalbuphine in management of pain

**Hemodynamic impact:** Compared to other analgesics, nalbuphine exhibits higher hemodynamic stability and analgesic efficacy, making it a top option for the management of postoperative pain [7]. This shows that nalbuphine may play a vital role in keeping cardiovascular parameters within ideal ranges throughout the crucial period following surgery, hence promoting improved patient outcomes.

Opioid-blocking and analgesic effects are two of nalbuphine's dual mechanisms of action as an agonist and antagonist opioid. Its morphine-like analgesic potency highlights its effectiveness in managing pain in a variety of clinical settings [8, 9]. Nalbuphine differs from traditional opioids due to its unique dual action, which may provide a more balanced method of pain management with fewer adverse effects.

**Depression of the respiratory system:** Notable is the ceiling impact of nalbuphine for this condition. It becomes more difficult to cause further respiratory depression after a certain point. This feature, along with its proven analgesic effectiveness, makes nalbuphine an attractive choice for pain management, especially as it has a lower risk of respiratory depression than conventional opioids [10]. This quality becomes especially important when respiratory issues need to be taken into account.

**Adverse effects:** When compared to morphine, nalbuphine exhibits less side effects, such as nausea, pruritus, and respiratory depression, because of its distinct mixed agonist-antagonist opioid receptor activity [10]. This implies that nalbuphine might reduce the typical negative effects of opioid analgesics while still providing efficient pain relief, improving the patient experience both during and after. This shows that nalbuphine may reduce the typical negative effects of opioid analgesics while effectively relieving pain, making patients' experiences both during and after medical operations more positive.

### Comparison with other analgesic

Nalbuphine was found to be a very effective analgesic for routine in-patient ENT procedures in a clinical review evaluating different analgesics used in ENT surgery. The study found that nalbuphine was one of the most effective analgesics for standard in-patient ENT surgery when given as a single intravenous bolus during anaesthesia induction, outperforming other analgesics in terms of analgesic effectiveness and postoperative pain relief [11]. Compared to other analgesics, nalbuphine shown less side effects, which made it a better choice for pain control during ENT procedures. The research emphasised the need of carefully choosing analgesics for regular ENT surgery while taking the consequences of the procedure, recovery, and postoperative care into account [11]. Additionally, a multimodal analgesic regimen that might include nalbuphine was evaluated for use in outpatient head and neck surgical procedures, and the results showed that the strategy was feasible, safe, and well-liked.

Additionally, a multimodal analgesic protocol that may include nalbuphine was evaluated for use in outpatient head and neck surgeries, and the results showed that the protocol was feasible, safe, and well-liked by patients having these operations [12]. For ENT procedures, nalbuphine has shown to be a highly effective and well-tolerated painkiller that works better than other analgesics while causing less side effects. It has been determined that including it into a multimodal analgesia protocol for outpatient head and neck surgical procedures is both possible and safe.

### Benefits and limitations of Nalbuphine in pain control

Using nalbuphine as a treatment for pain has clear benefits in a number of areas. First, it has proven to be effective in relieving pain without causing respiratory depression, which makes it a good option for treating paediatric patients' postoperative pain [12]. One other noteworthy feature is that it is able to maintain hemodynamic stability better than other analgesics such as morphine in this important regard [7]. This becomes more important when the patient's well-being depends on keeping their heart rate and blood pressure normal. Compared to patients receiving morphine, those given nalbuphine have demonstrated better analgesia, a better recovery profile, and more effective postoperative pain treatment [7].

Furthermore, the incidence of side effects linked to nalbuphine use is significantly lower than that of morphine and includes problems such as headache, dizziness, excessive sleepiness, hypertension, hypotension, arrhythmias, and skin rashes [7]. Moreover, certain characteristics of nalbuphine can be responsible for its lower risk of producing nausea and vomiting in comparison to morphine, which makes the postoperative period for patients more comfortable. Studies indicate that nalbuphine's distinct mixed agonist-antagonist opioid receptor activity, notably its kappa receptor agonism, may lessen gastrointestinal side effects, even though the precise mechanisms underlying this distinction need to be further clarified [7].

It is important to remember, though, that despite this apparent benefit, research is still being done on the evidence that nalbuphine is an effective analgesic, particularly when compared to other widely used opioids [12]. Furthermore, nalbuphine's intrinsic antagonist activity may restrict its analgesic benefits in some situations, with careful

consideration of how it may interact with spinal and epidural opioids<sup>[10]</sup>. Therefore, even if nalbuphine appears to have potential in lowering nausea and vomiting, these subtleties must be taken into consideration. To fully comprehend its limitations and relative usefulness in various clinical scenarios, more research is necessary.

### **Nalbuphine's impact on cardiovascular parameters**

#### **Control of Blood Pressure**

**Systolic and diastolic effects:** Nalbuphine was found to be able to avert a notable increase in heart rate and mean arterial pressure in a study investigating the hemodynamic response to orotracheal intubation<sup>[13]</sup>. Nalbuphine did not significantly affect heart rate or systolic blood pressure, according to another study, although it did cause a 35-minute drop in diastolic blood pressure. The decreases were found to be statistically significant 75 and 105 minutes after the dose<sup>[14]</sup>.

According to a different study, nalbuphine successfully avoids the significant rise in mean arterial pressure that is linked to orotracheal intubation and laryngoscopy<sup>[13]</sup>. Nalbuphine was found to raise mean arterial pressure in a comparison study with morphine, with a more noticeable increase noted in the nalbuphine group at particular intervals<sup>[16]</sup>. Nalbuphine has a complex influence on mean arterial pressure that might change based on the individual circumstances and patient attributes.

#### **Modulation of Heart Rate**

**No discernible effect on heart rate:** Results from a study<sup>[16]</sup> provided a thorough analysis of the hemodynamic response to orotracheal intubation, and they showed that nalbuphine did not significantly affect heart rate. This finding was supported by another investigation, which found that nalbuphine did not significantly change systolic blood pressure or heart rate<sup>[14]</sup>.

#### **Reduced blood pressure at the diastolic stage**

Within 35 minutes of dosing, nalbuphine demonstrated a significant reduction in diastolic blood pressure, however it had no effect on heart rate. This decrease showed a clear effect on this hemodynamic parameter, reaching statistical significance 75 and 105 minutes after delivery<sup>[14]</sup>. Attenuation of tachycardia: Studies have shown that nalbuphine is effective in lowering tachycardia, hypertension, and cardiac workload related to laryngoscopy and endotracheal intubation<sup>[16]</sup>. While nalbuphine doesn't seem to have much of an impact on heart rate, in certain circumstances it can be effective in reducing diastolic blood pressure and tachycardia, which is indicative of its complex hemodynamic effects.

#### **Vasomotor reactions**

The impact of nalbuphine on vasomotor reactions has been studied in relation to tracheal intubation and laryngoscopy. One study that compared equipotent dosages of pethidine, nalbuphine, and tramadol found that nalbuphine only decreased the inotropic response to airway instrumentation<sup>[17]</sup>. Furthermore, nalbuphine has been shown in another study to be an effective means of reducing the tachycardia, hypertension, and cardiac strain that are related to laryngoscopy and endotracheal intubation<sup>[16]</sup>. Nevertheless, within three minutes of nalbuphine administration, this same study found a non-significant drop in heart rate and all three

blood pressure indicators (systolic, diastolic, and mean arterial pressures). Its strong and pronounced kappa agonistic activity may be the cause of this observation<sup>[16]</sup>. The vasomotor response to laryngoscopy and pethidine, nalbuphine, tramadol, and a placebo were examined in another study.

### **Evidence and Clinical Research on Nalbuphine in ENT Procedures**

In patients having ENT operations, a research evaluating the effectiveness of 0.5 mg/kg pethidine and 0.2 mg/kg ketamine showed that both medications were efficacious at the indicated levels. Nevertheless, nalbuphine's superiority over other medications as an anti-shivering agent is not supported by enough data<sup>[18]</sup>. With a longer time to re-medication and a moderate emetic effect, nalbuphine has proven to be an effective sedative with analgesia throughout recovery. Interestingly, there was no evidence of respiratory depression for any of the analgesics investigated<sup>[11]</sup>. Two trials comparing nalbuphine and morphine have been conducted in paediatric patients following ENT procedures. For moderate-to-severe pain at one hour, the results revealed a non-significantly decreased or equivalent risk ratio<sup>[19]</sup>.

In a different study, nalbuphine was found to provide better hemodynamic stability, analgesia, recovery profile, and postoperative pain reduction than morphine for both intraoperative and postoperative analgesia. Additionally, nalbuphine decreased the frequency of nausea and vomiting<sup>[7]</sup>. Nalbuphine has a well-established track record of overall efficacy in sedation with analgesia throughout recovery, as well as advantages over other analgesics in ENT procedures with regard to hemodynamic stability, analgesia, recovery, and fewer side effects. Its clinical relevance is further supported by its particular efficacy in paediatric patients and the potential for enhanced analgesic effects when paired with other analgesics.

#### **Future directions**

Even with the wealth of studies on the use of nalbuphine in ENT procedures, several areas still need to be looked at. Examining the synergistic effects of nalbuphine in combination with other analgesics or anaesthetics is one possible direction for future research. For example, nalbuphine and droperidol together have a synergistic effect that reduces spontaneous movements in children during the induction of anaesthesia with propofol, according to a research published in the Journal of Clinical Anaesthesia<sup>[20]</sup>. The advantages of mixing nalbuphine with other medications to increase its analgesic effects or lessen negative side effects could be explored in more detail. Exploring the potential of nalbuphine's applicability to surgical specialties other than ENT procedures is another encouraging avenue for future research. While extensively studied in ENT surgeries, the potential advantages of nalbuphine in fields such as orthopedics or general surgery have yet to be thoroughly explored. Further research could evaluate the efficacy and safety of nalbuphine in these alternative surgical contexts. Finally, there is a need for more research to comprehend the long-term effects of nalbuphine use comprehensively. Despite indications that nalbuphine has fewer adverse effects compared to other analgesics, its extended impact on patient's health and recovery remains inadequately studied. Subsequent research endeavors could investigate the potential long-term

consequences of nalbuphine use, especially in patients necessitating repeated surgeries or prolonged pain management.

### Potential Improvements in Nalbuphine Administration

**Formulation modifications:** The development of slow-release or extended-release nalbuphine formulations can improve its bioavailability and reduce the need for frequent use. This breakthrough could lead to better pain management and possibly less negative side effects <sup>[21]</sup>.

**Dosage modifications:** Improving nalbuphine dosage schedules offers a way to better manage pain and reduce adverse effects. For example, a research showed that preemptive nalbuphine, at a dose of 0.2-1 mg·kg, was safe and effective in lowering visceral discomfort following surgery <sup>[22]</sup>. Subsequent investigations may determine the ideal dosage schedule for various surgical situations and patient demographics.

**Co-administration with other medications:** It has been shown that using nalbuphine along with other medications, including morphine, can effectively slow down the onset of morphine tolerance <sup>[23]</sup>. This cooperative strategy may improve the overall analgesic effect while lowering the possibility of addiction or dependence.

Other methods of administration. To improve nalbuphine bioavailability, alternate administration methods as rectal or oral delivery could be investigated. Furthermore, patients may find that these alternate ways provide a more practical and accessible way to receive the medication <sup>[21, 24]</sup>.

**Dosing according to the patient:** Customising the dosage of nalbuphine based on the weight, age, and unique response to the medication of each patient is one way to maximise pain management while reducing adverse effects.

Personalised medicine techniques used to nalbuphine dosage may result in more accurate and efficient pain control methods. Research is needed to determine the safest and most effective ways to provide nalbuphine to patients in a variety of surgical scenarios in order to fully investigate the benefits of patient-specific dosing <sup>[10]</sup>.

### New Developments in Analgesia for ENT Procedures

Preemptive analgesia, non-opioid analgesics, and nerve stimulation therapy are new advancements in ENT surgery. Preemptive analgesia with nalbuphine and dexamethasone effectively reduced postoperative pain in paediatric otolaryngology patients, according to a randomised controlled experiment <sup>[25]</sup>. NSAIDs and other non-opioid analgesics have demonstrated the ability to somewhat alleviate postoperative vomiting and control pain in comparison to opioids <sup>[25]</sup>. A potentially effective treatment for obstructive sleep apnea is hypoglossal nerve stimulation therapy, often known as upper airway stimulation <sup>[26]</sup>. This novel technique improves airway blockage by stimulating the hypoglossal nerve while you sleep by wrapping an electrode around it <sup>[26]</sup>. Additionally, patient-specific dosage and other personalised medicine approaches to analgesia show promise for maximising pain control while reducing side effects <sup>[27]</sup>. To summarise, the current state of analgesia for ENT procedures is focused on improving pain control, minimising side effects, and reducing the need for opioids.

### Conclusion

Finally, a thorough analysis of the literature on the hemodynamic effects of nalbuphine during ENT procedures reveals a number of important conclusions. Studies show that nalbuphine affects heart rate and blood pressure during ENT procedures; these effects vary depending on the patient's characteristics and dosage. Even though the overall evaluation points to a beneficial effect on hemodynamic stability, it is crucial to take into account the subtle differences among patient demographics and the possibility of interactions with various analgesics or anaesthetics frequently used in ENT procedures.

Notable practical consequences for clinical practice indicate that nalbuphine can help maintain stable hemodynamics when added to anaesthesia procedures. To guarantee safe and efficient use, nevertheless, the ideal dosage and any potential drawbacks need to be taken into consideration. In order to improve our knowledge of nalbuphine's function in enhancing clinical outcomes in ENT procedures and provide the groundwork for future developments in anaesthesia management, this review emphasises the significance of continuing research.

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