Pharmacological features, therapeutic efficacy and side effects of Nalbuphine: A review.

ABSTRACT:

Introduction: Opioids can provide effective analgesia and routinely utilized to treat mild severe pain. Problems related with mu- agonist opioids like nausea, emesis, bowel and bladder disturbances, respiratory depression, pruritus and developing tolerance and dependence. This article will review about the utilization of Nalbuphine, which is a mixed opioid agonist- antagonist that FDA has indicated in moderate to severe pain treatment when an opioid drug is essential and alternative treatment methods have failed. The incidence of the common opioid side effects are low in case of Nalbuphine. Non-FDA approved uses of nalbuphine are in labor analgesia, pruritus associated with opioid, opioid-induced urinary retention and respiratory depression. It can be administered with the regularly utilized mu- opioid agonists like morphine, fentanyl etc. as a combination , giving better analgesia along with abating the incidence as well as the severity of side effects caused by mu-agonist.

Methodology: This review article was prepared after a thorough study of the literature using data search engines such as 'Scopus',' PubMed', 'Web of Science', and 'Google Scholar'. This article referred to prior Nalbuphine observational studies and case reports.

Review findings: After learning the pharmacology, uses, contraindications of Nalbuphine and reviewing the previous observational studies and case reports about Nalbuphine, the drug can be used for treating moderate to severe pain when an opioid drug is essential and reserve treatment methods have failed. Nalbuphine finds its use also in labor analgesia. The incidence of the usual side effects due to opioids are low in case of Nalbuphine. It can be administered with the regularly utilized mu-opioid agonists like morphine, fentanyl etc. as a combination , giving better analgesia along with abating the incidence as well as the severity of side effects caused by mu-agonist.

Conclusion: Nalbuphine can be utilized for treating moderate to severe pain, as an adjuvant to balanced anesthesia for pre-operative / post-operative pain relief, for labor analgesia and to treat/ reduce the opioid induced side effects.

Keywords: Mu-receptor, Kappa-receptor, mixed agonist–antagonist, Nalbuphine, Opioid side effects

INTRODUCTON:

Nalbuphine hydrochloride is a synthetic phenanthrene derivative analgesic, which is a mixed opioid agonist-antagonist. Chemically it is shows similarity with both Naloxone (an opioid antagonist) and oxymorphone (a strong opioid analgesic). Nalbuphine is ideally FDA indicated for treating moderate to severe pain when an opioid drug is essential and reserve treatment methods did not work. With its use, the incidence of usual opioid adverse effects is low. Non-FDA approved uses of nalbuphine are in labor analgesia, pruritus associated with opioid, opioid-induced urinary retention and respiratory depression. It can be given in combination with routinely utilized mu- opioid agonists like fentanyl, morphine etc, and giving better pain relief along with prevention of the incidence as well as the severity of side effects caused by mu-agonist.

Chemical Properties:

- Nalbuphine is chemically a synthetic phenanthrene derivative.

- Nalbuphine hydrochloride is chemically 17-(cyclobutylmethyl)- 4,5α-epoxymorphinan-3,6α,14-triol hydrochloride.

- Molecular formula is: $C_{21}H_{27}NO_4 \cdot HCl$.

- The molecular weight of Nalbuphine hydrochloride is 393.91

- It is water soluble (35.5 mg/mL @ 25ºC) and also soluble in ethanol (0.8%);

And it is not soluble in CHCl3 and ether.

- The pKa values of Nalbuphine hydrochloride: 8.71 and 9.96.

PHARMACOLOGY:

Mechanism of Action: Nalbuphine shows agonistic action at kappa-opioid receptor and it has a partial antagonistic action at mu-opioid receptor. The analgesic characteristics showed by Nalbuphine are mediated by its agonist activity t the kappa-opioid receptor. When compared to morphine, Nalbuphine imparts pain relief with less incidence of pruritis, nausea and respiratory depression as a result of its unusual opioid receptor activity (mixed agonist-antagonist)[1]

Pharmacokinetics:

- Absorption: The onset of action is
  - 2 to 3 mins post IV injection.
  - Within 15 mins post intramuscular or subcutaneous injection.
- The duration of nalbuphine's action ranges from 3 to 6 hours.
- Metabolism: in the liver.
- Elimination: T ½ Elimination is about 5 hours. Its excretion is via faeces and urine.

Pharmacodynamics:

- On the Central Nervous System
  - The direct effect on the brain's respiratory centers leads to respiratory depression.
  - Nalbuphine causes miosis
- On the Gastro-intestinal (GI) Tract and on smooth Muscle
  - GI motility is reduced and tonicity of smooth muscle in the antrum of the alimentary canal (stomach and duodenum)is increased
  - Reduction in biliary secretions and pancreatic secretions
  - Can cause 'Sphincter of Oddi' spasm
- On the Cardiovascular System
  - Bradycardia
  - Orthostatic hypotension and syncope due to peripheral vasodilation
- On the Endocrine System
  - Adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) secretions are all suppressed.
  - The release of glucagon and insulin by the pancreas, as well as the secretion of growth hormone (GH) and prolactin are all stimulated.

INDICATIONS:

- For treating moderate to severe pain where an opioid drug is essential and alternative treatment methods have failed
- As an adjuvant to balanced anesthesia, for pre-operative as well as post-operative pain relief.
- Labor analgesia:
  - The addition of Nalbuphine in epidural labor analgesia can
    a) Amplify the local analgesic effect,
    b) Decrease the dose of local anesthetic , and
    c) Lessen the motor blockade
- On account of its antagonistic activity at the mu-opioid receptor , Nalbuphine reduces the opioid induced side effects like

- Pruritus [2]
- Emesis or Nausea
- Reduced bowel movements ,pain or difficulty in passing stools
- Inability to urinate, Frequent urination or loss of bladder control
- Hypoventilation and sedation
- Tolerance and dependence

ADMINISTRATION:

- Nalbuphine is acceptable for intravenous , intramuscular or subcutaneous injection
- It is available to us as 10 mg per mL and 20 mg per mL concentrations of nalbuphine hydrochloride
- Due to poor oral bioavailability of Nalbuphine, it is not suitable for oral route [5]
- It has a potency which can be compared to that of Morphine (on a mg-to-mg basis).[6]

Adult dosing:

- The recommended dose for a 70 kg person is 10 mg.
- The route of administration can be intravenous , intramuscular or subcutaneous
- Dose can be given every 3 to 6 hours if required.
- In case of opioid non-tolerant individuals, the single maximal dose recommended is 20mg with 160mg as a maximal daily dose.
- The dose shall be lessened by 25% in candidates with opioid-dependency; also, they must be monitored for signs or symptoms of opioid withdrawal.

Pediatric dosing:

- Safety and efficacy is not established in pediatric age group under less than one year of age
- 0.1 to 0.2 mg/kg body weight intravenously, intramuscularly, or subcutaneously in children with more than one year age, the dose can be repeated every 3 to 4 hours if required.

Note: Use cautiously with titrated dose in case of renal and liver disease (reduction in dose should be done)

ADVERSE EFFECTS:

Sedation, nausea/vomiting, dry mouth, sweating, dizziness, vertigo, headache etc are the commonest adverse effects seen after nalbuphine use.[7]

- Central nervous system:
  - Anxiety,
  - mentally depressed,
  - disorientation,
  - euphoria,
  - floating,
  - hostility,
  - restlessness
  - giddiness,
  - dysphoria,

- delusions,
- tingling and numbness

- Cardiovascular:
  - Blood pressure: may Increase or decrease
  - Heart rate: may Increase or decrease
- Gastrointestinal:
  - Abdominal pain and cramps,
  - heartburn ,
  - indigestion,
  - tastelessness
- Respiratory:
  - Shortness of breath
  - difficulty in breathing
- Dermatologic:
  - itching,
  - burning,
  - urticaria.
- Allergic Reactions: have been reported with nalbuphine use.[8]
  - anaphylactic,
  - anaphylactoid, or
  - severe hypersensitivity reactions

CAUTIONS IN USING NALBUPHINE:

- While administering nalbuphine along with benzodiazepines, alcohol or any CNS depressive drugs, it may lead to deep sedation and respiratory depression, which can result in coma, and death.
- Use Nalbuphine with utmost caution in those patients with history of head injury, those who are having elevated intracranial pressure and intracranial lesions because the carbon dioxide retention caused due to the respiratory depressant effects of nalbuphine will lead to further elevation of intracranial pressure in these patients. Also because of its sedative qualities, it hampers the accurate neurological evaluation in these patients.
- If nalbuphine is used for labour analgesia in the laboring woman, fetal heart rate must be monitored as there are reported events of severe fetal bradycardia post use of nalbuphine. [9]
- In patients who are on sustained-release opioids, withdrawal symptoms are seen after the administration of nalbuphine, because of its antagonist action at the μ-opioid receptor. So in these patients dose reduction is advised while using nalbuphine and further they must be observed for any withdrawal signs. [10]
- Impaired renal or hepatic function

CONTRAINDICATIONS:

- Patients with respiratory depression
- In known case of bronchial asthma, COPD

- In Known or suspected case bowel obstruction
- Allergic or history of hypersensitivity to nalbuphine/ opioids

Antidote: Intravenous naloxone

METHODOLOGY:

This review article was prepared after a thorough study of the literature using data search engines such as 'Scopus',' Pubmed', 'Web of Science', and 'Google Scholar'. This article referred to prior Nalbuphine observational studies and case reports.

REVIEW FINDINGS:

Khalid Maudood Siddiqui and Ursula Chohanin in 2007 compared intravenous tramadol with intravenous nalbuphine in patients posted for minor surgeries using total intravenous anesthesia technique using a propofol infusion and concluded that nalbuphine group patients were hemodynamically stable with better postoperative analgesia and recovery in comparison with tramadol group patients.[11]

Alon E etal in 1992, compared analgesic efficacy and applicability of the nalbuphine with tramadol and observed the postoperative pain score on the visual analogue scale and concluded that, PCA supplement were less and general well-being of the patients improved for the nalbuphine group.[12]

Diana Moyao-García et al in 2009, compared the effectiveness as well as the safety of Tramadol (IV) and Nalbuphine (IV) for postoperative pain management in children. They observed albuphine group showed more sedation whereas vomiting was more in tramadol group. [13]

Thomas J. Gal et al in 1982 when compared the respiratory depressing actions and analgesic of nalbuphine and morphine concluded that nalbuphine shows ceiling effects for respiratory depression.[14]

WT Beaver and GA Feisein 1978 studied the efficacy of analgesics in relation to one another between IM nalbuphine and IM morphine on postoperative patients. They found that nalbuphine was 0.8-0.9 times potent as compared to that of morphine.[15]

Naseer Bashir et al in 2017 did an observational study in participants posted for surgery under general anesthesia, the hemodynamic stability to laryngoscopy and endo-tracheal intubation were compared between IV Fentanyl and IV Nalbuphine, and it was found that fentanyl appeared to be better than nalbuphine.[16]

Bhot and colleagues in 2017 studied the analgesic effectiveness of nalbuphine IV, fentanyl IV and pentazocine IV as opioid analgesics for postoperative pain relief in minor general surgical procedures. They concluded that Nalbuphine, provides good postoperative analgesia in minor general surgical patients as compared to fentanyl and pentazocine, hence useful in day care surgeries .[17]

J. G. Brock-Utne et al, in 1985, compared intramuscular nalbuphine in a dose of 20 mg with intra muscular pethidine 100mg in patients after elective orthpaedic surgery and concluded that nalbuphine had a longer duration of action than pethidine.[18]

Zucker et al in 1987 compared nalbuphine with butorphanol to assess the respiratory depression in patients undergoing procedure under general anesthesia. They concluded that butorphanol caused significantly pronounced respiratory depression compared to that caused by nalbuphine. [19]

Lefevre et al in 1993 conducted a study to compare efficacy and side effects of nalbuphine and fentanyl as IV analgesics in patients scheduled for oral surgery under local anesthesia .The study

concluded that analgesia and sedation appeared sufficient and comparable but respiratory rate and oxygen saturation were significantly low in fentanyl group patients.[20]

Vidhya N et al after comparing the efficacy of butorphanol with nalbuphine for balanced anesthesia and post-operative analgesia in patients posted for laparoscopic surgery concluded that Butorphanol is more efficacious as an analgesic with better hemodynamic stability than Nalbuphine.[21]

Swapna Banerjee and Shaswat Kumar Pattnaik compared postoperative analgesia with epidural nalbuphine, butorphanol and fentanyl in lower abdominal surgeries concluded that fentanyl produces the faster onset of analgesia and Butorphanol gives longer duration of analgesia.[22]

V.V Lokeswari et al compared intra muscular nalbuphine with intramuscular butorphanol for postoperative pain relief concluded that intramuscular nalbuphine group patients were hemodynamically stable with better postoperative analgesia.[23]

Praveen P.V.V.S.B et al when IM nalbuphine, butorphanol, and pentazocine were tested for post-operative analgesia in patients having abdominal hysterectomy, concluded that nalbuphine and butorphanol offered superior analgesia than pentazocine.[24]

JJ Wang et al. compared analgesic efficacy of epidural butorphanol, nalbuphine, Meperidine and morphine concluded that both epidural nalbuphine and butorphanol demonstrated a very similar analgesic profile and when compared to morphine they exhibit faster onset of action with shorter duration.[25]

Viviane et al after comparing nalbuphine and butorphanol, either alone or in conjunction with acepromazine, it was found that butorphanol provided superior sedation than nalbuphine when used alone or in combination with acepromazine.[26]

F. N. Minai and F. A. Khan in 2003, After comparing intravenous nalbuphine to intravenous morphine for intra operative and postoperative pain relief in patients, posted for total abdominal hysterectomies under general anesthesia, concluded that nalbuphine gave superior analgesia with more stable haemodynamics than morphine.[27]

Jitesh kumar et al in 2017 compared IV Nalbuphine with IV Tramadol in participants undergoing minor surgical operations under TIVA. They found that Nalbuphine has superior analgesic properties than Tramadol for postoperative analgesia in minor surgical operations after finding that tramadol patients experienced higher postoperative nausea and vomiting.[28]

Neha Sharma et al n 2014 conducted a study to compare hemodynamic responses to intubation between IV Nalbuphine and IV Fentanyl . They discovered that there was an increase in B.P. was substantially higher in the Nalbuphine group, hence they suggested that Fentanyl be used instead of Nalbuphine.[29]

Rekha N Solanki et al in 2015 evaluated the post-operative analgesic properties and adverse effects of IV Nalbuphine and IV Tramadol in patients scheduled for orthopedic procedures under regional, general, or combined anesthesia. They determined that patients in the Nalbuphine group had superior post-operative analgesia and were more hemodynamically stable.[30]

Kiran K S et al in 2018 examined the effectiveness and safety of a single dose IV Nalbuphine versus IV Tramadol in adult participants posted for planned surgeries under general anesthesia for postoperative analgesia. They arrived at a conclusion that both Nalbuphine and Tramadol offered good post-operative analgesia, however Tramadol patients had a higher incidence of nausea and vomiting[31]

Hussain et al in 2016 compared the mean intake of commensurable dosages of IV Tramadol and IV Nalbuphine for the 1st 12 hrs of postoperative pain management in participants posted for

gynecological laparotomies, following anesthesia induction, all participants were administered with a loading dose of 1.5 mg/kg of Tramadol or 0.15 mg/kg of Nalbuphine. And as a baseline infusion these same drug was carried on; When the visual analogue scale (VAS) score was less than 3, a bolus of tramadol 0.5 mg/kg or nalbuphine 0.05 mg/kg was given. The total bolus dosage was computed and compared. Both the study drugs were administered as a bolus just before the commencement of operation and then continued as a continuous infusion afterward, they found that tramadol required smaller equipotent dosages of analgesic than nalbuphine for the management of breakthrough pain.[32]

Kamath SS et al in 2013 did a comparative study to assess the analgesic effectiveness of IV Nalbuphine with IV tramadol in patients scheduled for elective surgery under general anesthetic. They determined that Nalbuphine is a better painkiller than tramadol for the alleviation of moderate to severe postoperative pain and Nalbuphine provides better sedation. [33]

Tariq MA et al in 2014 investigated the effectiveness of nalbuphine in avoiding a hemodynamic response to laryngoscopy and oro-tracheal intubation. Subjects undergoing general anesthesia received a 0.2 mg/kg IV bolus dose of saline or nalbuphine 5 minutes before to laryngoscopy. After laryngoscopy and oro-tracheal intubation, the nalbuphine group had a considerably lower increase in mean arterial pressure (MAP) and heart rate (HR) than the control group.[34]

FA Khan et al in 1997 selected patients undergoing laparoscopic cholecystectomy under total intravenous anesthesia (TIVA) with propofol infusion. They compared IV Nalbuphine and IV buprenorphine and according to them, both medicines should be used to supplement total intravenous anesthesia with appropriate analgesics.

Priti M Chawda et al in 2010 investigated the efficacy of nalbuphine in reducing increases in heart rate (HR) and mean arterial pressure in response to laryngoscopy and oro-tracheal intubation. Patients received a 0.2 mg/kg IV bolus dose of saline or nalbuphine 5 minutes before laryngoscopy. They found that a dose of 0.2 mg/kg of Nalbuphine avoided a significant increase in heart rate (HR) and mean arterial pressure (MAP) during laryngoscopy and oro-tracheal intubation.[36]

Ahsan-ul-Haq et al in 2005 did a study to see how effective nalbuphine is at preventing heart rate (HR) and blood pressure (BP) increases while laryngoscopy and oro-tracheal intubation. They came to the conclusion that IV Nalbuphine (0.2 mg/kg) could avoid a significant increase in HR (heart rate) and MAP(mean arterial pressure) during laryngoscopy and oro-tracheal intubation.[37]

Shehla Shakooh et al in 2014 did a study to see how intrathecal nalbuphine affected pain alleviation in adult patients who were divided into two groups following lower limb and lower abdomen procedures. Intrathecal, one group received 0.5 percent hyperbaric bupivacaine while the other group was given 0.5 percent hyper baric bupivacaine (heavy)+ 0.8 mg of nalbuphine (preservative free) intra thecally. They came to the conclusion that nalbuphine given intra thecally increased the quality of intra operative and postoperative pain relief while causing few side effects.[38]

Aparna Jayara et al in 2018 examined the analgesic effects of intrathecal nalbuphine (1 mg) and tramadol (25 mg) in patients posted for vaginal hysterectomy under spinal anesthesia with 15 mg 0.5 percent hyperbaric bupivacaine in a research published in 2018. They concluded that nalbuphine has a faster onset and peak of analgesia than tramadol, and that nalbuphine and tramadol have statistically equal postoperative analgesia.[39]

B Jyothi et al examined the pain relieving effects of separate dosages of nalbuphine hydrochloride (0.8, 1.6, and 2.5 mg) with bupivacaine(15 mg) given intrathecal and bupivacaine(15 mg)alone given intrathecal for lower abdomen and orthopedic operations. In comparison to 1.6 and 2.4 mg of nalbuphine, they found that inclusions of 0.8 mg nalbuphine to 0.5 percent bupivacaine in SAB (sub arachnoid block) gives superior analgesia with a longer duration of effect.[40]

Bhavini Shahand et al in 2019 compared the safety and analgesic effectiveness of nalbuphine 20mg to tramadol 100mg as an adjuvant to 0.5 percent bupivacaine for supraclavicular block. When compared to tramadol as an additive, they found that adding nalbuphine to 0.5 percent bupivacaine in supraclavicular brachial plexus block considerably accelerates the onset and prolongs the duration of sensorimotor blockade and analgesia. In terms of safety, both medications were comparable.[41]

ParveezTaneja et al in 2019 for treating shivering post-anesthesia after spinal anesthesia in Caesarian section, they compared the anti-shivering effect of tramadol IV to nalbuphine IV and saline as placebo. They came to the conclusion that nalbuphine and tramadol have similar anti-shivering effects.[42]

Dr. Vishma et al in 2016 selected patents posted for upper limb procedures, tramadol 100mg and nalbuphine 10mg were compared as adjuvants to 0.5 percent lignocaine for day care IVRA in them. Tramdol and Nalbuphine and as adjuvants to lignocaine in intravenous regional anesthesia ended up in sooner onset and lengthening of the duration of sensory as well as motor blocks with no major problems, and nalbuphine had the longest postoperative analgesia duration time..[43]

Fareed Ahmed et al in 2016 did a study in participants scheduled for abdominal hysterectomy under SAB to assess the potentiating impact of intrathecal nalbuphine with 15 mg of 0.5 percent hyperbaric bupivacaine for postoperative analgesia in three different doses (0.8mg, 1.6mg, and 2.4mg). They observed that combining bupivacaine with nalbuphine for intrathecal administration notably extended postoperative pain relief when compared to the control group, with the best outcomes coming from a 1.6 mg dose of nalbuphine given intrathecally.[44]

Shagufta Naaz et al in 2017 compared the analgesic effects of nalbuphine and fentanyl given intrathecally as adjuvants in lower limb orthopedic surgery . The participants were given 12.5 mg 0.5 percent injectable bupivacaine heavy, as well as 25 g 0.5 ml fentanyl, 0.8 mg 0.5 ml nalbuphine, or 1.6 mg 0.5 ml nalbuphine. They observed that nalbuphine hydrochloride (0.8 mg and 1.6 mg) and fentanyl (0.8 mg and 1.6 mg) prolong sensory blockade, give excellent quality, and provide prolonged postoperative analgesia. Intrathecal fentanyl or 1.6 mg nalbuphine have no substantial advantage over low dose 0.8 mg nalbuphine. They found that 12.5% injectable bupivacaine heavy with 0.8 mg 0.5 ml nalbuphine was the most effective of the three groups.[45] Studies on post-operative analgesic efficacy of nalbuphine were reported by Dalal et. al. [46] and Gantasala et. al. [47].

CONCLUSION:

Nalbuphine can be utilized in treating moderate to severe pain, as an adjuvant to balanced anesthesia for pre-operative and post-operative pain relief, for labor analgesia and to treat/ reduce the opioid induced side effects.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES:

1) Davis MP, Fernandez C, Regel S, McPherson ML. Does nalbuphine have a niche in managing pain? J Opioid Manag. 2018 Mar/Apr;14(2):143-151.
2) Jannuzzi RG. Nalbuphine for Treatment of Opioid-induced Pruritus: A Systematic Review of Literature. Clin J Pain. 2016 Jan;32(1):87-93
3) Schmidt WK, Tam SW, Shotzberger GS, Smith DH, Clark R, Vernier VG. Nalbuphine. Drug Alcohol Depend. 1985 Feb;14(3-4):339-62
4) Baxter AD, Samson B, Penning J, Doran R, Dube LM. Prevention of epidural morphine-induced respiratory depression with intravenous nalbuphine infusion in post-thoracotomy patients. Can J Anaesth. 1989 Sep;36(5):503-9
5) Davis MP, McPherson ML, Mehta Z, Behm B, Fernandez C. What Parenteral Opioids to Use in Face of Shortages of Morphine, Hydromorphone, and Fentanyl. Am J Hosp Palliat Care. 2018 Aug;35(8):1118-1122.
6) Errick JK, Heel RC. Nalbuphine. A preliminary review of its pharmacological properties and therapeutic efficacy. Drugs. 1983 Sep;26(3):191-211
7) Chrétien B, Dolladille C, Hamel-Sénécal L, Sassier M, Faillie JL, Miremont-Salamé G, Lelong-Boulouard V, Le Boisselier R, Fedrizzi S, Alexandre J, Humbert X. Comparative study of hypoglycaemia induced by opioids. Is it a class effect? Expert Opin Drug Saf. 2019 Oct;18(10):987-992.
8) Dinges HC, Otto S, Stay DK, Bäumlein S, Waldmann S, Kranke P, Wulf HF, Eberhart LH. Side Effect Rates of Opioids in Equianalgesic Doses via Intravenous Patient-Controlled Analgesia: A Systematic Review and Network Meta-analysis. Anesth Analg. 2019 Oct;129(4):1153-1162.
9) Nicolle E, Devillier P, Delanoy B, Durand C, Bessard G. Therapeutic monitoring of nalbuphine: transplacental transfer and estimated pharmacokinetics in the neonate. Eur J Clin Pharmacol. 1996;49(6):485-9
10) Opioids for pain. Med Lett Drugs Ther. 2018 Apr 09;60(1544):57-64.
11) Siddiqui KM, Chohan U. Tramadol versus Nalbuphine in total intravenousanesthesia for Dilatation and Evacuation. J Pak Med Assoc2007;57:67-70
12) Alon E, Atanassoff PG, Biro P.Intravenous postoperative pain management usingnalbuphine and tramadol. Anaesthesist 1992 Feb;41(2):83-87.
13) Moyao-Garcia D, Hernandaz-Palacios JC, Ramfrez-Mora JC, . Nava-ocampa AA. A pilot studyofnalbuphine versus tramadol administered through continuous intravenousinfusion for postoperative pain control in children. Acta Biomed. 2009;84:124-130.
14) Gal TJ, DiFazio CA, Moscicki J. Analgesic and Respiratory Depressant Activity ofNalbuphine; A comparison with Morphine. Anesthesiology1982;57:367-364
15) Beaver WT, Feise GA. A comparison of the analgesic effect of intramuscularnalbuphine and morphine in patient with postoperative pain. Pharmacology andExperimental Therapeutics.1978;204(2):487-496.
16) Naseer Bashir Khanday,AshokChowdhary,NanditaMehta,SahirRasool.A Comparative Study of Fentanyl AndNalbuphine on Hemodynamic Response to Laryngoscopy And Endotracheal Intubation In Patients Undergoing Surgery Under General Anesthesia. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 10 Ver. XI (Oct. 2017), PP 72-77
17) *Bhot, Priyanka, Preeti R. More and Damayanti Shah. A comparative study of nalbuphine, fentanyl and pentazocine as intravenous analgesics for postoperative pain relief in minor general surgical procedures. Indian journal of applied research 7 (2017): n. pag.*
18) Brock – Utne J.G, Ritchie P, .Downing J.W. A comparison of nalbuphine and pethidine for postoperative pain relief after orthopaedicsurgery.SAfr Med J 1985; 68:391-393.
19) Zucker JR, Neuenfeldt T, Freund PR. Respiratory effects of nalbuphine and butorphanol in anesthetized patients. Anesth Analg1987;66:879-81.

20) Lefevre B, Freysz M, Lepine J, Royer JM, Perrin D, Malka G. Comparison of nalbuphine and Fentanyl as intravenous analgesics for medically compromised patients undergoing oral surgery. Anesth Prog1993;39:13-8
21) Comparative efficacy of butorphanol versus nalbuphine for balanced anesthesia and post-operative analgesia in patients undergoing laparoscopic surgery :Vidhya N, Prakash V, Irshad B, V. S. Senthil Kumar
22) A comparative between epidural butorphanol , nalbuphine and fentanyl for postoperative analgesia in lower abdominal sugeries ; SWARNA BANERJEE, SHASWAT KUMAR PATTNAIK
23) A comparative study of intra muscular nalbuphine with intramuscular butorphanol for the relief of postoperative pain ; Dr.V.VLokeswari. Dr. B.AnnapurnaSarma, Dr.D.B.V.Madhusudhana Rao.
24) A prospective , randomized , double blind , comparative study of intramuscular nalbuphine hydrochloride, butorphanol tartrate and pentazocine lactate for postoperative pain relief following abdominal hysterectomy; Praveen P.V.V.S.B., Vijaya Chandra Reddy Konda , Lohit K
25) Comparative analgesic efficacy of epidural nalbuphine, butorphanol, Meperdine and morphine; JJ Wang, MS Mok and M Lippmann
26) Comparison of the sedative effects of nalbuphine and butorphanol , alone or in combination with acepromazine in dogs ; Viviane et al.
27) Minai FN, Khan FA. A Comparison of Morphine and Nalbuphine for Intraoperative and Postoperative Analgesia. J Pak Med Assoc 2003;53: 391-6.
28) Jitesh Kumar, P.K. Sinha, B.K. Prasad , Ajay Simbha. Comparative study of Nalbuphine and Tramadol for postoperative pain relief in patients of short surgical procedures under TIVA. International journal of contemporary medical research 2017;ISSN(online): 2393-915X, (print):2454-7379,volume 4, issue 4(Apil 2017)
29) Neha Sharma ,Hetal Parikh.A comparative study of hemodynamic responses to intubation:fentanyl versusnalbuphine .GUJARAT MEDICAL JOURNAL / AUGUST-2014 Vol. 69 No. 2: 48-53
30) *Rekha N Solanki , Nita D Gosai ,Geeta M Joshi, Bipin M. Patel ,Honey Modi and Reena Jain.*A Comparative Study of Intravenous NalbuphineHCl and Tramadol HCl for Post- Operative Pain Relief Following OrthopaedicSurgeries.Asian Pacific journal of Health Sciences ,2015;2(1):155-160
31) Kiran K S, Vyas V, Patil S. Comparative efficacy and safety of intravenous tramadol and nalbuphine for pain relief in postoperative patients. Indian J Pain 2018;32:96-101
32) Hussain, T., Ahmad, S., Taqi, A., &Khwaja, S. (2016). A COMPARISON OF EQUIPOTENT DOSES OF TRAMADOL AND NALBUPHINE IN GYNECOLOGICAL LAPAROTOMIES POSTOPERATIVELY. *Pakistan Armed Forces Medical Journal*, *66*(5), 738-41.
33) Shaila S Kamath, Arun Kumar BC, Madhusudan Upadya, Sonal Bhat.A Comparison of the Analgesic Effect of Intravenous Nalbuphine and Tramadol in Patients with Post-operative Pain - a Double Blind Prospective Randomised Study.Asian Journal of Pharmaceutical and Health Sciences,2013,3,3,786-790.
34) AM, Iqbal Z, Qadirullah . Efficacy of nalbuphine in preventing haemodynamic response to laryngoscopy and intubation. Journal of postgaraduate medical institute 2014;28(2):211-216
35) Khan FA, Zaidi A.Kamal RS. Comparison of nalbuphine and buprenorphine in total intravenous anesthesia.Anesthesia1997;52:1095-1101
36) Priti M Chawda, Mayuresh K Pareek, and Ketan D Mehta.Effect of Nalbuphine on Haemodynamic Response to Orotracheal Intubation. Journal of anaesthesiology clinical pharmacology.2010 Oct-Dec; 26(4): 458–460

37) Ahsan-ul-Haq M, Kazmi EH and Rao ZA .Nalbuphine prevents haemodynamic response to endotracheal intubation.Journal of the College of Physicians and Surgeons--pakistan : JCPSP, 01 Nov 2005, 15(11):668-670
38) ShehlaShakooh, Pooja Bhosle.Intrathecal Nalbuphine: An Effective Adjuvant ForPostoperative Analgesia.Innovative Journal of Medical and Health Science 4: 2March–April(2014)79-82.
39) *Jayara, A., Bhandari, G., &Shahi, K.S. (2018). Comparative study of analgesic effect of intrathecal nalbuphine and tramadol in patients undergoing vaginal hysterectomy. International Journal of Biomedical and Advance Research, 9, 136-141.*
40) *Jayara, A., Bhandari, G., &Shahi, K.S. (2018). Comparative study of analgesic effect of intrathecal nalbuphine and tramadol in patients undergoing vaginal hysterectomy. International Journal of Biomedical and Advance Research, 9, 136-141.*
41) Bhavini Shah, Guneet Chadha, Ashwini Khamborkar. Comparative Evaluation of Nalbuphine and Tramadol as an Adjuvant to 0.5% Bupivacaine in Supraclavicular Brachial Plexus Block. Indian J AnesthAnalg. 2019;6(5):1511-1516.
42) ParveezTaneja, Yogesh Bansal, Nidhi Sharma,Kewal Krishan Banotra. A randomized control trial for comparison among Nalbuphine, Tramadol and placebo for treating post anesthetic shivering undergoing spinal anesthesia in CessariansectionJ. Pharm. Sci. & Res. Vol. 11(5), 2019, 2095-2098
43) Dr. Vishma K, Dr. Divya Vincent.Comparison of 0.5% Lignocaine with Tramadol and with Nalbuphine for Day Care IVRAin Upper Limb: anInterventional StudyIOSR Journal of Dental and Medical Sciences (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 9 Ver. VIII (September). 2016), PP 99-105
44) Ahmed F, Narula H, Khandelwal M, Dutta D. A comparative study of three different doses of nalbuphine as an adjuvant to intrathecal bupivacaine for postoperative analgesia in abdominal hysterectomy. Indian J Pain 2016;30:23-8
45) ShaguftaNaaz, Usha Shukla, Swati Srivastava, ErumOzair and AdilAsghar.A Comparative Study of Analgesic Effect of Intrathecal Nalbuphine and Fentanyl as Adjuvant in Lower Limb OrthopaedicSurgery.Journal of Clinical and Diagnostic Research,2017 Jul; 11(7): UC25–UC28.
46) Dalal, Shivani Tejas, and Sanjot Ninave. "Postsurgical Analgesic Efficacy of Epidural Nalbuphine in Lower Abdominal Surgeries." JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS 9, no. 4 (January 27, 2020): 216–22. https://doi.org/10.14260/jemds/2020/50.
47) Gantasala, Bhargav Vishnu, Amol Singam, Saranya Rallabhandi, Kashish Chaubey, Pallavi Deulkar, and Ayush Pal Bansal. "Comparison of Intrathecal Dexmedetomidine and Nalbuphine as an Adjuvant in Hyperbaric Bupivacaine for Saddle Block and Postoperative in Patients Perianal." JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS 9, no. 29 (July 20, 2020): 2028–33. https://doi.org/10.14260/jemds/2020/442.