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Research Article

Comparison of Effectiveness of Nalbuphine and Ondansetron in Preventing the Complications of Spinal Morphine

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Abstract

Intrathecal Morphine (Spinal Morphine) is an excellent postoperative Analgesic. But there are some adverse effects associated with this which we have to deal with. These are Pruritus, Nausea & Vomiting. Pruritus is commonest. Respiratory depression can also happen but it is rare. We have done study on I.v Ondansetron and Nalbuphine which can prevent these side effects. These were used alone and in combination.

Introduction

Morphine is the opioid very commonly used for postoperative pain control. It is administered by several routes. The advantage of intrathecal (IT) morphine over intravenous (IV), oral (PO), or transdermal (TD) opiates is due to its delivery into the sub-arachnoid space with direct access to opiate receptors and ion channels. Optimal pain control may decrease complications and facilitate recovery during immediate postoperative period. Optimal pain control can be achieved by a multimodal technique which may include regional techniques, systemic or neuraxial opioids, non-steroid anti-inflammatory drugs and centrally acting drugs like paracetamol. The first published report on IT administration of morphine was by a Romanian surgeon, Racoviceanu-Pitest, who presented his experience using a mixture of cocaine and morphine in 1901, in Paris. In 1977, Wang et al described the efficacy of IT morphine for postoperative analgesia in a group of eight patients with genitourinary malignancy in 1979. Since then, the use of IT morphine has become widely acceptable technique. Morphine was the first opioid approved by the United States Food and Drug Administration (FDA) for its neuraxial use and perhaps it is the most widely neuraxially used opioid. This study looks into some of the key aspects of the use of IT morphine for postoperative analgesia and study drugs which can prevent complications.

Intrathecally administered morphine must be preservative-free, sterile, nonpyrogenic, and free of antioxidants and other potentially neurotoxic additives. When drawing up intrathecal morphine from a glass vial, a filter needle is necessary as small glass particles can be catastrophic to neural tissue when administered into the intrathecal space.

Use of intrathecal morphine requires close attention to dosing as the potency of the morphine is dramatically enhanced by intrathecal delivery. The recommended bolus dose for intraoperative and postoperative analgesia is 0.1 to 0.2 mg intrathecally.

Clinical Uses of Intrathecal Morphine

- Labor analgesia
- Perioperative analgesia for intra-abdominal, intra-thoracic, and orthopedic surgery of the lower extremities
- Perioperative analgesia for Cesarean section
- Severe chronic pain in patients who have not obtained adequate analgesia from more conservative therapies

Pharmacology of Morphine

Morphine is an opiate found in opium, the juice secreted by the seedpods of poppies. It is a potent pain reliever and is similar in structure to other opiate analgesics.

Mechanism of Action : Opioid Receptors

Morphine binds to opioid receptors, molecular signalling activates the receptors to mediate certain actions. There are three important classes of opioid receptors and these are:

- μ receptor or Mu receptors - There are three subtypes of this receptor, the μ1, μ2 and μ3 receptors. Present in the brainstem and the thalamus, activation of these receptors can result in pain relief, sedation and euphoria as well as respiratory depression, constipation and physical dependence.
- κ receptor or kappa receptor - This receptor is present in the limbic system, part of the forebrain called the diencephalon, the brain stem and spinal cord. Activation of this receptor causes pain relief, sedation, loss of breath and dependence.
- δ receptor or delta - This receptor is widely distributed in the brain and also present in the spinal cord and digestive tract. Stimulation of this receptor leads to analgesic as well as antidepressant effects but may also cause respiratory depression

Pharmacokinetics: Morphine can be administered orally, intravenously, rectally, subcutaneously, through spinal injection (e.g. intrathecal, epidural) as well as through inhalation or snorting. The drug has a significant amount intrathecal, of first pass metabolism in the liver with only around 40 to 50% of the amount absorbed actually reaching the nervous system. Most of the morphine is processed in the kidneys and eliminated from the body in urine.

Adverse effects of morphine

Morphine has many side effects. Some of the more common and more dangerous ones include:

- Nausea, vomiting and abdominal cramps
- Constipation
- Sedation and drowsiness
- Itching and allergic skin reactions causing warmth and flushing
- Shrinking of the pupils to pin points
- Respiratory depression or suppressed breathing
- Initial doses lead to euphoria but higher doses cause unpleasant symptoms such as hallucinations, delirium, dizziness and confusion
- Formation of physical or psychological dependence and development of withdrawal symptoms when use of the drug is stopped
- Development of tolerance and the need to increase dose to achieve the same degree of effects as before
- Risk of overdose and poisoning
- Transmission of HIV/AIDS and hepatitis B and C among needle users.

Pharmacology of Ondansetron

Ondansetron is a highly potent and selective antagonist at 5HT3 receptors. Its anti-emetic actions were first revealed by its ability to antagonize retching and vomiting induced by chemotherapy and radiotherapy in

animals and man.

Subsequently, the availability of labelled 5-HT3 receptor ligands allowed identification of 5-HT3 receptors, located at highest densities in the area postrema, nucleus tractus solitarius (NTS), in other areas of the brain, and on afferent terminals of the vagus nerve. Postoperative nausea and vomiting may be caused by various factors: the anaesthetic, associated drugs, the surgical procedure, movement of the patient, sex, weight and pain. These factors mediate their effects via the higher brain circuits, the vestibular nuclei, the chemoreceptor trigger zone in the area postrema, or the upper gastrointestinal tract via the vagus nerve, influencing motor and visceral emetic outputs in the hind-brain. It is hypothesized that ondansetron blocks nausea and vomiting by 5-HT3 receptor antagonism at two specific sites: (i) centrally, in the area postrema/NTS; and (ii) peripherally on vagus nerve terminals. The absence of other pharmacological effects of ondansetron ensures an absence of side-effects.

Indications In the adult patient population: i) orally administered ondansetron tablets and orally disintegrating tablets (ODT) are indicated for: - the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy, including high dose cisplatin therapy, and radiotherapy, and - the prevention and treatment of postoperative nausea and vomiting.

Pharmacodynamics: Ondansetron is a highly specific and selective serotonin 5-HT3 receptor antagonist, not shown to have activity at other known serotonin receptors and with low affinity for dopamine receptors4. The serotonin 5-HT3 receptors are located on the nerve terminals of the vagus in the periphery, and centrally in the chemoreceptor trigger zone of the area postrema. The temporal relationship between the emetogenic action of emetogenic drugs and the release of serotonin, as well as the efficacy of antiemetic agents, suggest that chemotherapeutic agents release serotonin from the enterochromaffin cells of the small intestine by causing degenerative changes in the GI tract. The serotonin then stimulates the vagal and splanchnic nerve receptors that project to the medullary vomiting center, as well as the 5-HT3 receptors in the area postrema, thus initiating the vomiting reflex, causing nausea and vomiting.

Moreover, the effect of ondansetron on the QTc interval was evaluated in a double-blind, randomized, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron was tested at single doses of 8 mg and 32 mg infused intravenously over 15 minutes.

At the highest tested dose of 32 mg, prolongation of the Fridericia corrected QTc interval (QT/RR0.33=QTcF) was observed from 15 min to 4 h after the start of the 15 min infusion, with a maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction of 19.6 (21.5) msec at 20 min. At the lower tested dose of 8 mg, QTc prolongation was observed from 15 min to 1 h after the start of the 15-minute infusion, with a maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction of 5.8 (7.8) msec at 15 min. The magnitude of QTc prolongation with ondansetron is expected to be greater if the infusion rate is faster than 15 minutes. The 32 mg intravenous dose of ondansetron must not be administered. No treatment-related effects on the QRS duration or the PR interval were observed at either the 8 or 32 mg dose.

An ECG assessment study has not been performed for orally administered ondansetron. On the basis of pharmacokinetic pharmacodynamic modelling, an 8 mg oral dose of ondansetron is predicted to cause a mean QTcF increase of 0.7 ms (90% CI 2.1, 3.3) at steady-state, assuming a mean maximal plasma concentration of 24.7 ng/mL (95% CI 21.1, 29.0). The magnitude of QTc prolongation at the recommended 5 mg/m2 dose in pediatrics has not been studied, but pharmacokinetic pharmacodynamic modeling predicts a mean increase of 6.6 ms (90% CI 2.8, 10.7) at maximal plasma concentrations.

In healthy subjects, single intravenous doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. Multi day administration of ondansetron has been shown to slow colonic transit in healthy subjects.

Pharmacology of Nalbuphine

Nalbuphine, is an opioid analgesic. It is agonist/antagonist opioid modulator. Specifically, it acts as a moderate-efficacy partial agonist or antagonist of the μ-opioid receptor and as a high-efficacy partial agonist of the κ-opioid receptor, whereas it has relatively low affinity for the δ-opioid receptor and sigma receptors. Nalbuphine was patented in 1963 and was introduced for medical use in the United States in 1979.

Pharmacodynamics; Nalbuphine is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis, which is based on relative potency studies using intramuscular administration (Beaver et al. 1978). Oral administered nalbuphine is reported to be three times more potent than codeine (Okun et al. 1982). Clinical trials studied single dose experimental oral immediate release nalbuphine tablets for analgesic efficacy over a four- to six-hour time period following administration.

Nalbuphine in the 15 to 60 mg range had similar analgesic effects to immediate release codeine in the 30 to 60 mg range (Kantor et al. 1984; Sunshine et al. 1983). Schmidt et al. (1985) reviewed the preclinical pharmacology of nalbuphine and reported comparative data relative to other types of opioid compounds. The authors point out that the nalbuphine moiety is approximately ten times more pharmacologically potent than the mixed opioid agonist/antagonist butorphanol on an "antagonist index" scale which quantitates the drug's ability to act both as an analgesic (via opioid KOR agonism) as well as a μ-opioid receptor antagonist. The opioid antagonist activity of nalbuphine is one-fourth as potent as nalorphine and 10 times that of pentazocine.

Pharmacokinetics: The onset of action of nalbuphine occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection. The elimination half-life of nalbuphine is approximately 5 hours on average and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

Adverse Effects: Like pure μ-opioid receptor agonists, the mixed agonist/antagonist opioid class of drugs can cause side effects with initial administration of the drug which lessens over time (“tolerance”). This is particularly true for the side effects of nausea, sedation and cognitive symptoms (Jovey et al. 2003). These side effects can in many instances be ameliorated or avoided at the time of drug initiation by titrating the drug from a tolerable starting dose up to the desired therapeutic dose. An important difference between nalbuphine and the pure μ-opioid receptor agonist opioid analgesic drugs is the “ceiling effect” on respiration (but no ceiling on the analgesic effect). Respiratory depression is a potentially fatal side effect from the use of pure μ-opioid receptor agonists. Nalbuphine has limited ability to depress respiratory function (Gal et al. 1982).

As reported in the current Nubain Package Insert (2005), the most frequent side effect in 1066 patients treated with nalbuphine was sedation in 381 (36%).

Other, less frequent reactions are: feeling sweaty/clammy 99 (9%), nausea/vomiting 68 (6%), dizziness/vertigo 58 (5%), dry mouth 44 (4%), and headache 27 (3%). Other adverse reactions which may occur (reported incidence of 1% or less) are:

- CNS effects: Nervousness, depression, restlessness, crying, euphoria, flushing, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine.
- Cardiovascular: Hypertension, hypotension, bradycardia, tachycardia, pulmonary edema.
- Gastrointestinal: Cramps, dyspepsia, bitter taste.
- Respiration: Depression, dyspnea, asthma.
- Dermatological: Itching, burning, urticaria.
- Obstetric: Pseudo-sinusoidal fetal heart rhythm.

Other possible, but rare side effects include speech difficulty, urinary urgency, blurred vision, flushing and warmth.

Aims and Objectives

The aim of study was to compare the efficacy of preventing complications following spinal morphine by the prophylactic treatment with nalbuphine, ondansetron, combination of the two and no prophylaxis at all.

Materials and Methods

This study was done in ASA I to III 60 patients in age group from 18 to 80 years. These patients underwent following surgeries .

1-Knee Replacement,

2-Hip Replacement,

3-ACL Reconstruction,

4-Caesarian Section.

All patients were evaluated in the Anaesthesia Clinic 2 to 5 days prior to surgery. Full medical history was taken & allergies were documented. Routine investigations& ECG were done. If patient had any co-morbidity, appropriate referral & treatment was initiated.

All patients received Intrathecal Morphine in dose of 150 mcg to 00 mcg. All these patients received 0.5% Bupivacaine with Fentanyl 20 mcg as per protocol of Anaesthesia Department. These patients were divided into four groups as follows.

Group 1-No prophylaxis is be given after spinal morphine.

Group 2-Ondansetron 4mg iv is given within half an hour of the spinal or after the delivery of baby in Caesarean sections.

Group 3-Nalbuphine 2.5 mg IV is given within half an hour of spinal or after delivery of baby in Caesarean sections.

Group 4-Ondansetron 4mg IV and Nalbuphine 2.5mg IV are given within half an hour of spinal or after delivery of baby in Caesarean sections.

GROUP	NUMBER
Group 1 CONTROL	15
Group 2 ONDANSETRON	
Group 3 NALBUPHINE	
Group 4 ONDANSETRON AND NALBUPHINE	
TOTAL	

Patients were given Spinal Anaesthesia with full aseptic precautions using pencil point Spinal needle 27G. Within half an hour the prophylactic agent was administered. In Caesarian sections the agent was administered after baby was delivered and cord clamped. Routine monitoring of vitals was done. After Surgery patients were shifted to Post Anaesthesia Care Unit (PACU) & monitored for pruritus, nausea, vomiting & Respiratory Depression. Patients were shifted to the ward after 2 hours. In the ward monitoring of the patients continued. In the ward vital signs were recorded every hour for 12 hours and after that every two hours for next 12 hours. Patients were checked for pain, pruritus, nausea and vomiting. All patients received paracetamol 1een 12 and 24 hours the percentage of patients who complained of gm q6hrly as routine. If patients had breakthrough pain it was managed by Parecoxib 40 mg IV p.r.n

Observations

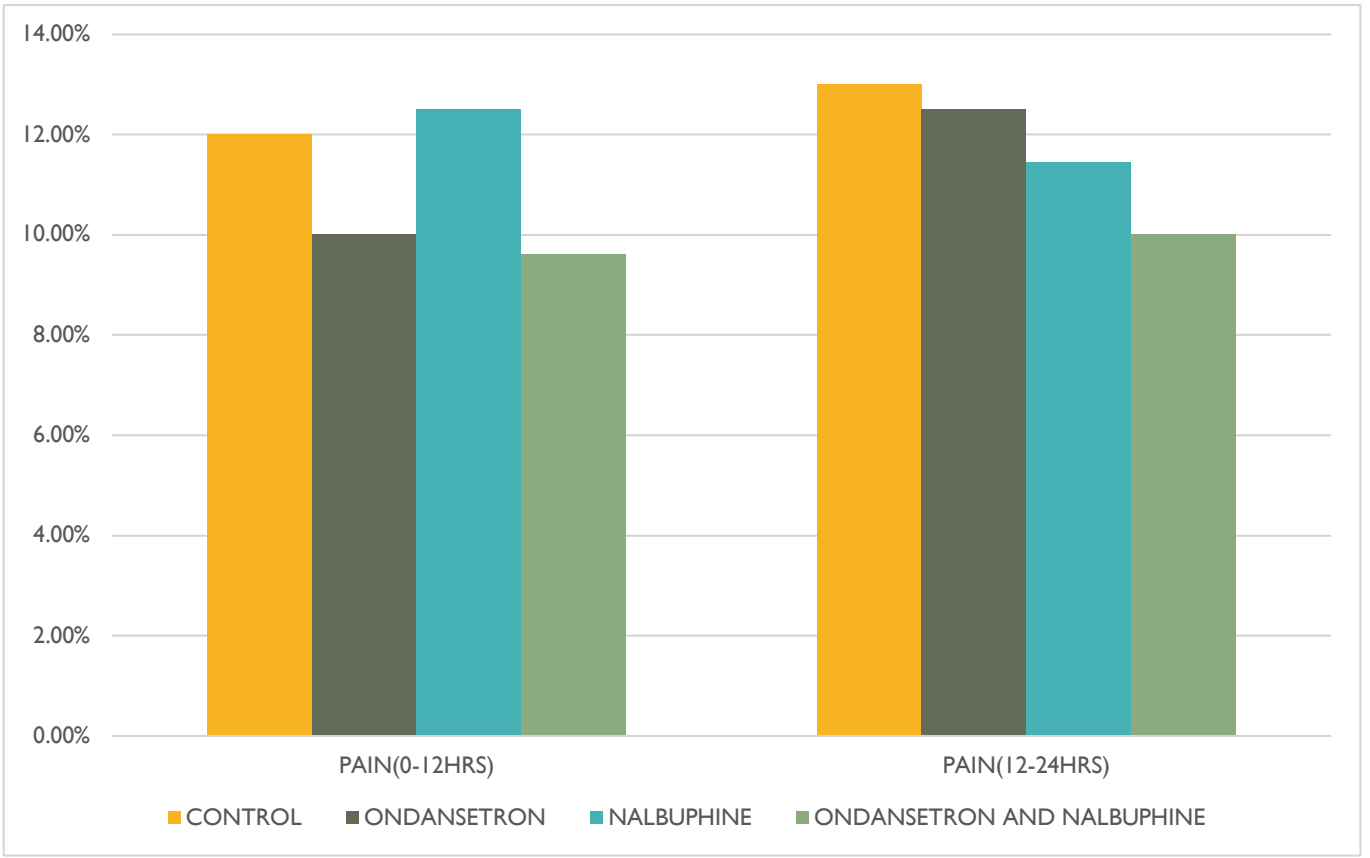
GROUPS	PAIN 0-12 HRS	PAIN 12-24HRS	PONV 0-12 HRS	PONV 12-24HRS	ITCHING 0-12 HRs	ITCHING 12-24 HRS	Respiratory Depression	ALLERGIC REACTIONS
1-CONTROL	12%	13%	6%	4%	4.38%	3.5%	0	0
2-ONDANSETRON	10.%	12.5%	1%	0%	3.5%	3	0	0
3.NALBUPHINE	12.5%	11.45%	4.5%	2%	0.5%	0.4%	0	0
4.ONDANSETRON AND NALBUPHINE	9.6%	10%	0.5%	0%	0%	0%	0	0

Pain After Spinal/ Intrthecal Morphine

The incidence of pain after spinal morphine in the groups within 12hr were 12% (control), 10%(ondansetron), 12.5%(nalbuphine), 9.6%(ondansetron and nalbuphine).

Between 12 and 24 hours pain was 13%(control), 12.5%(ondansetron), 11.45%(nalbuphine), 10%(both nalbuphine and ondansetron).

Percentage Of Pain After Spinal Morphine

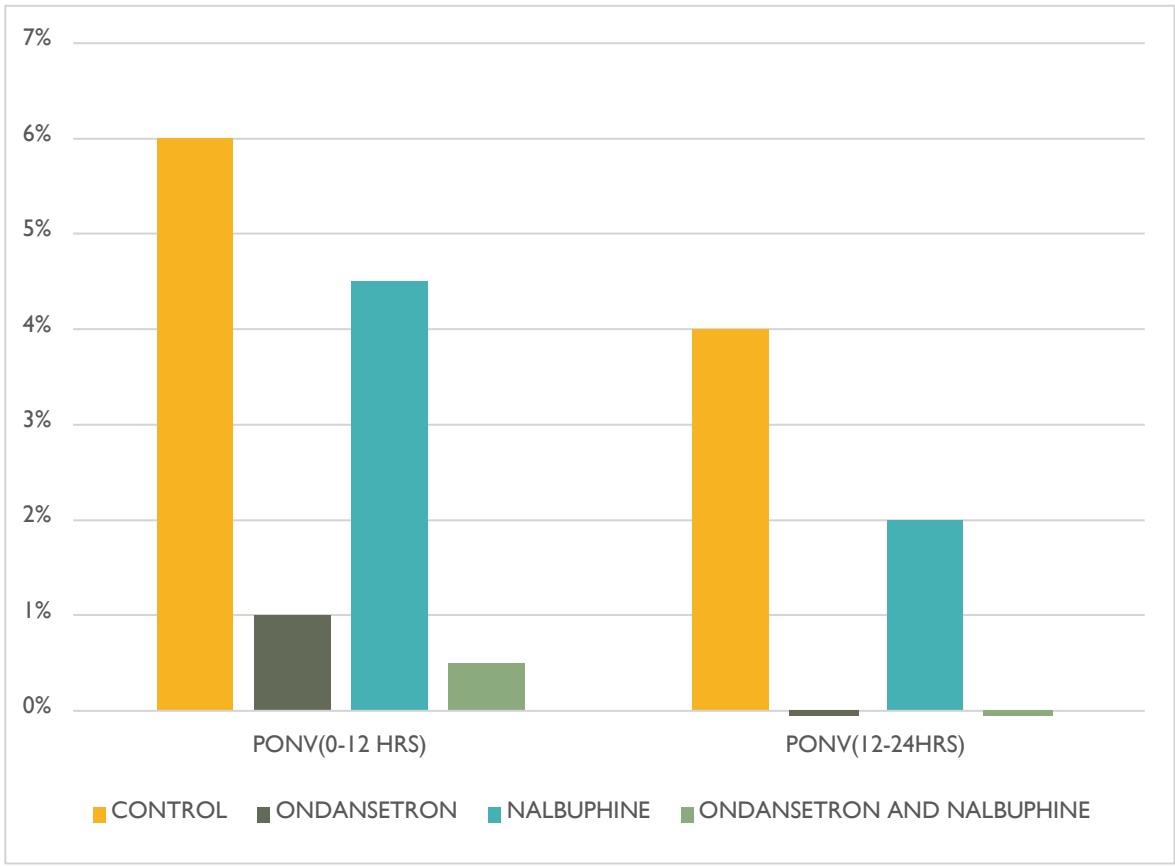


Postoperative Nausea and Vomiting (PONV)

The percentage of postoperative nausea and vomiting in the control group within 12 hours where no prophylactic medication was given was 6%. Ondansetron 1% and nalbuphine group 4.5% whereas in the group where both ondansetron and nalbuphine were given the percentage was 0.05%.

After 12 hours and within 24 hours after spinal morphine the postoperative nausea and vomiting in Control group was 4% , 0 in Ondansetron group 2% in Nalbuphine group. In the ondansetron and nalbuphine group it was 0%.

PONV After Spinal Morphine

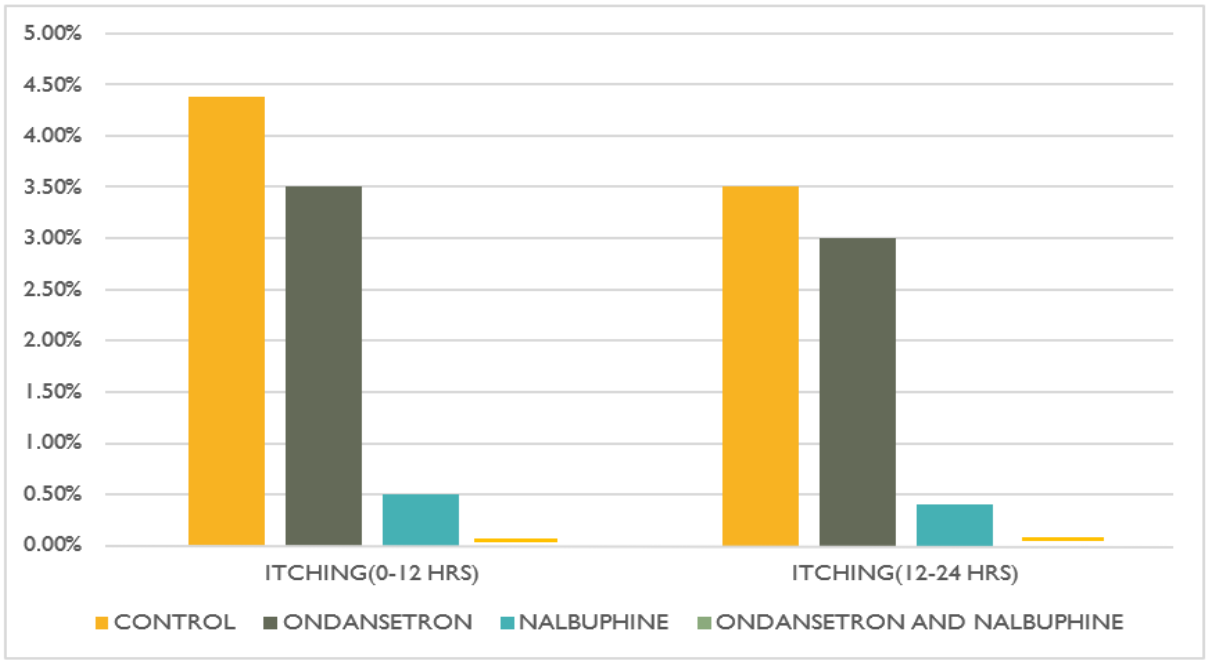


Pruritus (Itching)

The percentage of itching in the first 12 hours were 4.38%(control), 3.5% for ondansetron, 0.5% for nalbuphine group,0% for the group with the combined prophylaxis. In the next 12 hours it was 3.5% for control, 3% for ondansetron group, 0.4% for nalbuphine group but 0% for the combined prophylaxis.

Pruritus (Itching)

Percentage of Itching after Spinal Morphine



Respiratory Depression

None of the patients in any group had respiratory depression.

Other Complications

There were no other complications.

Discussion

Intrathecal morphine provides excellent postoperative analgesia but it's use is associated with some side effects. Pruritis is the most common complication with a reported incidence of 58-85%. The exact mechanism of morphine induced pruritus is unclear. Nalbuphine is an opioid agonist–antagonist and its analgesic and possible antipruritic effects are mediated via mu and kappa receptors. Many studies have shown the use of nalbuphine in treaingt the side effects of spinal morphine without reversing the analgesia.

Ondansetron, a selective antagonist at 5-HT3 receptors, commonly used for treatment of nausea and vomiting is effective in treating the side effects of spinal morphine like pruritus and nausea and vomiting.

Conclusion

The study entitled "Comparison of Effectiveness of Nalbuphine and Ondansetron in preventing the complications of Spinal.

Morphine" was conducted in a regional referral Hospital in the UAE.

"Intrathecal morphine produces excellent analgesia but there are side effects like pruritis, nausea & vomiting. These side effects can be reduced by prophylactic dose of IV Nalbuphine 2.5 mg & IV Ondansetron 4 mg combined, within half an hour of spinal morphine. In Caeserian Sections the drugs were administered after baby was out This is a limited study of 60 patients & larger trials will be needed to reinforce the use of ondansetron & nalbuphine in the perioperative period.

References

1. Yeh HM, Chen LK, Lin CJ, Chan WH, Chen YP, Lin CS, et al. Prophylactic intravenous ondansetron reduces the incidence of subarachnoid morphine induced pruritus in patients undergoing cesarean delivery. Anesth Analg. 2000;91:172–5. [PubMed]

2. Szarvas S, Harmon D, Murphy D. Neuraxial opioid-induced pruritus: A review. J Clin Anesth. 2003;15:234–9. [PubMed]

3. Somrat C, Oranuch K, Ketchada U, Siriprapa S, Thipawan R. Optimal dose of nalbuphine for treatment of intrathecal-morphine induced pruritus after caesarean section. J Obstet Gynaecol Res. 1999;25:209–13.[PubMed]

4. Charuluxananan S, Somboonviboon W, Kyokong O, Nimcharoendee K. Ondansetron for treatment of intrathecal morphine-induced pruritus after cesarean delivery. Reg Anesth Pain Med. 2000;25:535–9.[PubMed]

5. Charuluxananan S, Kyokong O, Somboonviboon W, Narasethakamol A, Promlok P. Nalbuphine versus ondansetron for prevention of intrathecal morphine-induced pruritus after cesarean delivery. Anesth Analg. 2003;96:1789–93. [PubMed]

6. Shah MK, Sia AT, Chong JL. The effect of the addition of ropivacaine or bupivacaine upon pruritus induced by intrathecal fentanyl in labour. Anaesthesia. 2000;55:1008–13. [PubMed]

7. Bonnet MP, Marret E, Josserand J, Mercier FJ. Effect of prophylactic 5-HT3 receptor antagonists on pruritus induced by neuraxial opioids: A quantitative systematic review. Br J Anaesth. 2008;101:pp311–9.[PubMed]

8. Bromage PR. The price of intraspinal narcotic analgesia: Basic constraints. Anesth Analg. 1981;60:461–3. [PubMed]

9. Bailey PL, Rhondeau S, Schafer PG, Lu JK, Timmins BS, Foster W, et al. Dose-response pharmacology of intrathecal morphine in human volunteers. Anesthesiology. 1993;79:49–59. [PubMed]

10. Krause L, Shuster S. Mechanism of action of antipruritic drugs. Br Med J (Clin Res Ed) 1983;287:1199–200. [PMC free article] [PubMed]

11. Kumar K, Singh SI. Neuraxial opioid-induced pruritus: An update. J Anaesthesiol Clin Pharmacol. 2013;29:303–7. [PMC free article] [PubMed]

12. Koju RB, Gurung BS, Dongol Y. Prophylactic administration of ondansetron in prevention of intrathecal morphine-induced pruritus and post-operative nausea and vomiting in patients undergoing caesarean section. BMC Anesthesiol. 2015;15:18. [PMC free article] [PubMed]

13. George RB, Allen TK, Habib AS. Prophylaxis of neuraxial opioid pruritus with 5HT3 antagonists: A systematic review. Anesthesiology. 2007;107:A1039.

14. Siddik-Sayyid SM, Aouad MT, Taha SK, Azar MS, Hakki MA, Kaddoum RN, et al. Does ondansetron or granisetron prevent subarachnoid morphine-induced pruritus after cesarean delivery? Anesth Analg. 2007;104:421–4. [PubMed]

15. Yeh YC, Lin TF, Chang HC, Chan WS, Wang YP, Lin CJ, et al. Combination of low-dose nalbuphine and morphine in patient-controlled analgesia decreases incidence of opioid-related side effects. J Formos Med Assoc. 2009;108:548–53. [PubMed]