Which Has Greater Analgesic Effect: Intrathecal Nalbuphine or Intrathecal Tramadol?

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Abstract: Nalbuphine and tramadol administered epidurally has been demonstrated to decrease postoperative analgesic requirements. However, its effect on postoperative analgesia after intrathecal administration has not will be established. In this double-blind, the effect of intrathecal tramadol and nalbuphine administration on pain control after gynecological surgery was studied. Sixty patients undergoing Transurethral resection of the bladder tumor were studied and randomized to receive bupivacaine 0.5% 3 ml intrathecally premixed with either tramadol 50mg [1ml],or nalbuphine 2mg[1ml].After operation, paracetamol IV (1gm) was administered as needed for analgesia. Postoperative analgesic requirements, visual analogue scale for pain (VAS) and sedation scores, times to first analgesic, haemodynamic parameters and side effects were recorded by a blinded observe. There were no differences between the groups with regard to postoperative requirements in the first 24hours. Also there were no significant differences as regard sensory level, duration of motor block in hours and time to receive first analgesic between the two groups. Sedation scores in tramadol group were significantly higher than nalbuphine group. The homodynamic changes were similar in both groups and the incidence of nausea and vomiting was higher in tramadol group. On conclusion, the intrathecal administration of 50 mg tramadol and intrathecal 2 mg nalbuphine when used with 0.5% bupivacaine had a similar the postoperative analgesia in the patients without producing significant related side effects like nausea, vomiting, pruritus and respiratory depression.
[Mostafa Galal Mostafa, Mohamad F. Mohamad and Waleed S.H.Farrag. Which Has Greater Analgesic Effect: Intrathecal Nalbuphine or Intrathecal Tramadol?. Journal of American Science 2011;7(7):480-484].(ISSN: 1545-1003). http://www.americanscience.org.

Keywords: Analgesic Effect; Intrathecal Nalbuphine; Intrathecal Tramadol

1. Introduction:

Transurethral resection of the bladder tumor is an operation leading to significant post operative pain and associated analgesic requirement and opioids are chosen for pain relief (Cohen et al, 1992). Intrathecal(IT) opioid administration has been demonstrated to provide effective postoperative analgesia after a variety of surgical procedures [Jacobson et al., 1988].

Although intrathecal morphine provides prolonged and excellent pain relief in various clinical settings [Wang et al., 1979 and Bailey et al., 1993], its use has been limited because of the dose-dependent risk of delayed respiratory depression which requires a close monitoring of respiratory patterns [Bailey et al., 1993].

Nalbuphine, a drug with mixed μ antagonist and κ agonist properties, has been used to prevent or treat these morphine-related adverse effects, especially after epidural administration of morphine [Alhashemi et al., 1997, Wittels etal., 1993 and Cohen et al., 1992]. The addition of intrathecal nalbuphine 0.4 mg to hyperbaric tetracaine, compared with intrathecal morphine 0.4 mg, for spinal anesthesia improved the quality of intraoperative and postoperative analgesia, with fewer side effects [Lin, 1992].

Tramadol is a centrally acting analgesic agent with a terminal elimination half-life of 5.5 hours and provides clinical analgesia for 10 hours after epidural administration [Vickers et al., 1992 and Tarkkila et al., 1998], as it has 6000 fold less affinity for μ receptors compared to morphine [Raffa et al., 1992 and Scott, 2000]. It also inhibits serotonin and norepinephrine reuptake in the spinal cord and has no reported neural toxicity [Tsai et al., 2001]. Inaddition, tramadol has the ability to provide effective postoperative analgesia with no risk of respiratory depression, pruritis, nausea, vomiting and urinary retention after central neuraxial administration (Douman et al., 2010).

Therefore, we undertook a prospective, randomized, double-blinded study to compare the analgesic effects and duration of analgesia as well as the side effects of 50 mg tramadol or 2 mg nalbuphine administered via the IT route for postoperative pain relief after transurethral resection tumor of the bladder.

There is little comparative data showing how post-operative analgesic effects differ between interathecal nalbuphine and interathecal tramadol.

The purpose of this study was to compare the analgesic effects of interathecal nalbuphine

(2mg), and interathecal tramadol (50mg) using analgesic demand and VAS pain scores.

2. Materials and Methods

After approved of the local ethics committee of South Egypt Cancer Institute, Assiut University, and written, informed consent was obtained from each patient, this prospective, randomized, double-blinded study was performed, 60 patients ASA class I - III under spinal anesthesia were recruited into this study. Patients who had a known allergy to nalbuphine or tramadol, Patients with a contraindication to spinal anesthesia or those who did not agree to participate in study were also excluded.

Patients were randomized to one of two study groups: intrathecal tramadol (group T) or intrathecal nalbuphine (group N) of 30 patients each.

Group T: In which we administered intrathecal mixture of 15 mg hyperbaric bupivacaine 0.5 % [3 ml] [Marcaine®, Astra] in addition to 50 mg [1 ml] of preservative free tramadol hydrochloride [October Pharma S.A.E] the final volume was 4 ml.

Group N:The patients had received intrathecal mixture of 15mg hyperbaric bupivacaine 0.5 % [3 ml] plus 2 mg of preservative free nalbuphine in 1 ml [nalbuphine HCL 20 mg (SERB, rue Villiers de llsle Adam 75020 Paris FRANC].

Patients and anesthesia providers were blinded to the treatment group. [The study drugs were prepared by another investigator not included in the patient care]. An IV infusion of lactated Ringer's solution 500 ml through a peripheral venous catheter was started. In all patients, electrocardiogram, noninvasive arterial blood pressure, and peripheral oxygen saturation were monitored at baseline and every 5 min thereafter until the end of surgery, and an indwelling urinary catheter was inserted at the end of the operation. The skin of the back was prepared in the usual fashion, and was anaesthetized locally with lidocaine 2% 3 ml at level L3-4 with the patient in the sitting position. Spinal puncture was performed using a 25-gauge pencil-point spinal needle. All patients received bupivacaine 0.5% 15 mg intrathecally, co-administered in a blinded fashion with either preservative-free tramadol 50 mg 1 ml [group T] or preservative-free nalbuphine 2mg 1 ml(group N).

Ephedrine 6 mg i.v was used as needed to treat hypotension (defined as a 20% decrease in systolic blood pressure from baseline value). HR <55 beats/min was treated with atropine 0.5 mg i.v as required. After surgery, patients were transferred to the recovery room until the next morning and received 4L oxygen by face mask. As soon as the pain score at the operative site was higher than 3 cm on the visual analogue scale (VAS, 0 cm no pain, 10 cm maximal pain), Pain score (VAS) assessed at 2,4,8,12,16 and 24 hours postoperative, respiratory rate, oxygen saturation, sedation score (1: awake and alert, 2: awake but drowsy, responding to verbal stimulus, 3: drowsy but rousable, responding to physical stimulus, 4: unrousable, not responding to physical stimulus) and hemodynamic changes were recorded. All patients remained in the recovery room for 24 h after their arrival paracetamol 1gm was given on the visual analogue scale higher than 3 cm, the time of first request of analgesia ,number of rescue analgesia,the duration of motor block from the time of drug administration to the time when patient was able to lift his leg and the adverse effects such as nausea, vomiting, pruritus, respiratory depression (respiratory rate =8 breaths/min) were recorded

Statistical analysis

Descriptive values are expressed as mean ±SD or number. The Student t-test was used for comparison between means of continues variables and normally distributed data, proportions were compared using Chi-squared or Fisher's exact test as appropriate otherwise Mann-Whitney U test was used. P was considered significant if ($p < 0.05$).

3. Results:

As shown in table (1), there were no significant differences between the two groups as regard age year, weight, height or operative time

The duration and degree of the block were equal for all patients except one patient in tramadol group who required general anesthesia supplementation in the form of inhalational halothane via laryngeal mask for completion of surgical procedure due to failure of spinal anesthesia. The mean maximal level of sensory block for tramadol group was T5±0.2 and to T6±0.1 for nalbuphine group. Comparison of mean values of visual analogue scores in both groups revealed significant ($p<0.05$) lower score in both groups at all readings (Fig 1.)

As shown in table (2), the mean time to first rescue analgesic was 8.5 ± 3.67 in nalbophine group versus7.35 ± 2.4 in tramadol group, sedation score was equal in both groups, number of rescue analgesia was small in nalbophine group and analgesic consumption (Paracetamol injection (gm/24h) was less in nalbophine group but this difference in these parameters was not significant ($p>0.05$) (Table 2).

As shown in table (3), the heart rate and mean blood pressure, they were stable with minimal variation, which were not significant. Four patient in the Tramadol group developed hypotension requiring treatment as opposed to two patients in Nalbuphine group. Seven patients had postoperative nausea and

vomiting in Tramadol group as opposed to three in Nalbuphine group. None of the patients had postoperative pruritus or respiratory depression (p>0.05) (Table 3).

Table 1. Patient Characteristic. Data are mean± (SD)

Variable	Group T (n=30)	Group N (n=30)
Age (yr)	68 ±8.1	66.23±9.2
Weight (kg)	64.51±3.18	66.51±4.1
Height (cm)	168±3.1	165±1.4
Operative time (min)	130.5±35.9	126±39.5
GA supplementation(N of patients)	1	0

Table 2 Sedation score and postoperative analgesia

Variable	**GroupT** (n=30)	**Group N** (n=30)
Maximal level of sensory block	T5±0.2	T6±0.1
Duration of motor block in hours	5.8±0.8	5.9±0.9
Sedation score	1.1 ± (0.2)	1.2 ± (0.3)
Time to first analgesia (Hours)	7.35 ± 2.4	8.5 ± 3.67
Number of rescue analgesia	2(0.6%)	1(0.3%)
Analgesic consumption Paracetamol injection(gm/24h)	2 gm	1 gm

Table 3: Side effects and hemodynamic changes

Variables:-	Group T (n=30)	Group N (n=30)
Nausea /vomiting	7(2.1%)	3 (0.9%)
Pruritus	0 (0%)	0 (0%)
Respiratory depression	0	0
Maximum change in MABP all over 24 hours(mmHg)	21±5	20±9
Maximum change in heart rate all over 24 hours (beat/min)	7±4	6±9

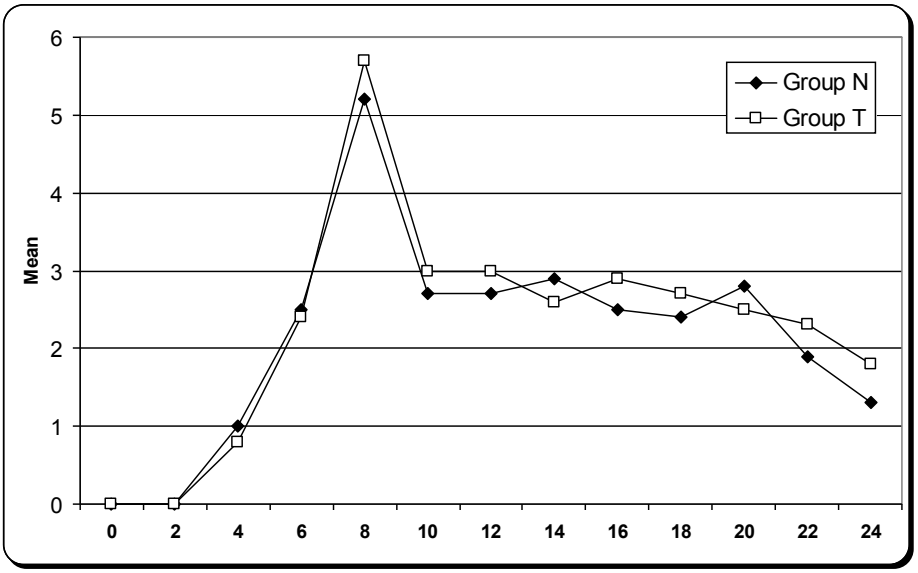

Fig. (1)VAS: Score versus Time for the two group

4. Discussion:-

Tramadol is a centrally acting analgesic agent with a terminal elimination half-life of 5.5 hours and provides clinical analgesia for 10 hours after epidural administration [Prosser et al, 1997]. Tramadol stimulates the μ- receptors and to a lesser extent the delta and kappa receptors. Although tramadol is one-fifth as potent as morphine as an analgesic, it causes less respiratory depression and pruritus (chakraborty et al., 2008).

Our results show that 2 mg interathecal nalbuphine had similar analgesic effects of 50 mg interathecal tramadol each of them prolonged the duration of post-operative analgesia and reduced VAS pain score. Also this study demonstrated that the interathecal tramadol (50mg) and intrathecal nalbuphine (2mg) with bupivacaine provides similar motor block in nalbuphine, and tramadol groups, nearly equal analgesia, delayed first analgesic request, less analgesic supplement, lower number of analgesic in the first 24 hours and the times to first analgesic request and the amounts of paracetamol administered over the first24 after operation were all comparable between the two study groups, which suggest that tramadol did not potentiate the local anaesthetic effects of bupivacaine.

Guduz and colleagues (2001), found that tramadol does not prolong the duration of action of bupivacaine when the drugs are co-administered caudally.

The effective intrathecal dose of tramadol is still confusing. Chakraborty et al.,(2008), has studied the effect of intrathecal tramadol (20mg) added to bupivacaine in patients undergoing major gynecological surgery and they found that the duration of analgesia provided by intrathecal administration of 20 mg tramadol with 15 mg of 0.5% hyperbaric bupivacaine was significantly longer than that provided by intrathecal bupivacaine alone.

Also they suggested using dose of 20mg of tramadol intrathecally with 15 mg of 0.5% hyperbaric bupivacaine can prolongs postoperative analgesia without serious adverse effects after major gynecological surgeries (chakraborty et al., 2008).

Wilder-Smith and colleagues (1998), suggest that epidural tramadol in a dose of 20 mg may have anti-analgesic effects. Alhshemi and Kaki (2003), reported that intrathecal tramadol (25mg) was not different from saline in its effect on postoperative morphine requirements after TURP and this may be due to dose used in this study could have been too small for a clinically relevant analgesic effect to be detected. Due to lipophilic properties of tramadol resulted in rapid diffusion of the drug out of the subarachnoid space. So, we used a large dose in this study

No Changes in haemodynamic variables or quality of analgesia after Intravenous tramadol 1.5 mg/kg and nalbuphine 0.1 mg/kg in total intravenous anaesthesia (TIVA) using a propofol infusion in patients undergoing dilatation and evacuation (Siddiqui and Chohan, 2007).

Fournier et al (2000), have demonstrated that after total hip replacement, administration of intrathecal nalbuphine resulted in a significantly faster onset of pain relief and shorter duration of analgesia than intrathecal morphine.

Xavier et al., (2000), suggested that intrathecal nalbuphine 0.8 mg provides good intra operative and early postoperative analgesia without side effect such as pruritis and postoperative nausea and vomiting and this allows earlier discharge of patients from the recovery room.

The addition of intrathecal nalbuphine 0.4 mg to hyperbaric tetracaine, compared with intrathecal morphine 0.4 mg, for spinal anesthesia improved the quality of intraoperative and postoperative analgesia, with fewer side effects (Lin, 1992). Intrathecal nalbuphine 0.8 –1.6 mg seems to improve the quality of intraoperative analgesia during cesarean deliveries and ncreasing the nalbuphine dose to 1.6 mg did not further improve analgesia due to this drug may have a ceiling effect above 0.8 mg due to its lipophilic properties (Wang et al., 1988).

Rawal et al (1991), showed, in a sheep model using histopathological methods, that intrathecal nalbuphine was not neurotoxic. Even large doses (15–24 mg) of intrathecal nalbuphine were not associated with histopathological changes of the spinal cord.

The hemodynamic variables and sedation score were comparable in the two groups in our study. Alhshemi and Kaki (2003), reported that intrathecal tramadol (25mg) did not seem to influence the intra operative haemodynamic profile of patients undergoing this type of anesthetic. These results are in keeping with those reported previously by other investigators who have demonstrated that parenteral tramadol does not have clinically relevant effects on HR and blood pressure [Tarkkila et al., 1997].

In this study seven patients in tramadol group and three patients in nalbuphine group had vomiting and none of the patients in both groups had postoperative complication like, itching, respiratory depression, neurological sequelae or complaints were observed until discharge of the patient from the hospital among the two groups. The incidence of hemodynamic side effects like decreased blood pressure, bradycardia, respiratory depression and other side effects like somnolence and dryness of mouth were minimum and well tolerated by the patients studied.

On conclusion, intrathecal administration of 50 mg tramadol and intrathecal 2 mg nalbuphine when used with 0.5% bupivacaine had a similar the postoperative analgesia in the patients without producing significant related side effects like nausea, vomiting, pruritus and respiratory depression and recommend a further study with a large dose in different surgical studies.

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6/27/2011