Original Article

Post operative analgesia after incisional infiltration of bupivacaine v/s bupivacaine with buprenorphine

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Abstract

Introduction: Opioid receptors have been demonstrated in the peripheral nerve endings of afferent neurons. Blockade of these receptors with peripherally administered opioid is believed to result in analgesia.

Aim: To evaluate whether buprenorphine added to bupivacaine for wound infiltration can enhance post-operative analgesia via peripheral mechanisms.

Materials and Methods: Forty ASA I and II adult patients scheduled for open donor nephrectomy were enrolled in this randomized double blind prospective study. In group A (n = 20) patients, the wound was infiltrated with bupivacaine 0.5% (2 mg/kg) and in group B (n = 20) with bupivacaine 0.5% (2 mg/kg) and buprenorphine (2 µg/kg). All patients were given diclofenac 75 mg IM at 8 h interval. Post-operative quality of analgesia was assessed by VAS (0-10) for 24 h and when VAS > 4 rescue analgesic was administered. Total dose of rescue analgesic and side effects were noted.

Results: The time of administration of first rescue analgesic was significantly higher in group B (10.52 ± 5.54 h) as compared to group A (3.275 ± 1.8 h). Mean VAS was significantly lower in group B as compared to group A. The total dosage of rescue analgesic was more in group A as compared to group B patients.

Conclusion: Addition of buprenorphine to the local anesthetic significantly prolonged the time to first rescue analgesic requirement and the total consumption of rescue analgesic in 24 h, thus providing evidence in support of the existence of peripheral opioid receptors.

Key words: Buprenorphine, post-operative analgesia, peripheral opioid receptors

Introduction

Opioids are more efficacious in inflammed tissues. Clinical trials have however not demonstrated consistent benefit with use of peripherally administered opioids in acute pain, except in intra-articular injection during surgery. The efficacy of opioids in inflammed tissue can possibly be used advantageously for management of post-operative pain. The aim of this study was to evaluate the hypothesis that combination of local anesthetic and opioid when injected in inflammed tissue can improve the quality of analgesia.[1,2]

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Materials and Methods

Forty ASA I and II adult patients scheduled for elective donor nephrectomy were enrolled in a randomized double blind prospective study after the hospital ethics committee approval and written informed consent. The study exclusion criteria included use of opioids during 24 h prior to study, drug, or alcohol abuse and H/O allergy to any of the study drug. A conventional balanced general anesthesia was administered. The induction protocol was standard for all patients and consisted of intravenous administration of glycopyrrolate (0.2 mg), fentanyl (2 µg/kg), thiopentone sodium (5-7 mg/kg), succinylcholine (1.5 mg/kg), and vecuronium (4 mg). Anesthesia was maintained with a mixture of nitrous oxide and oxygen, isoflurane, and supplements of vecuronium. Donor nephrectomy was performed in kidney position with 11th rib flank incision. The patients were randomly assigned to either of the two groups A and B (n = 20 patients each) by the closed envelope method.

At the end of the surgery in group A patients, the wound was infiltrated intradermally with bupivacaine 0.5% (2 mg/kg) and in group B infiltration was done with bupivacaine 0.5% (2 mg/kg) + buprenorphine (2 μg/kg). The solutions were diluted up to 20 cc with distilled water and given in two coded syringes to the surgeon for infiltration. All patients were given diclofenac 75 mg IM half an hour before extubation and at 8 h interval in the post-operative period. Post-operative pain was assessed by a blinded investigator using a 0-10 point Visual Analogue Scale (0-no pain, 10-unbearable pain). VAS > 4 was taken to indicate significant pain and used as a cut off point for rescue analgesia with tramadol 50 mg IV. Both the groups were compared for duration of analgesia (time from wound infiltration to time of administration of first analgesic) and total consumption of supplemental analgesic in 24 h. Signs of opioid side effects like drowsiness, nausea, vomiting, and pruritus were noted. Urinary retention was not evaluated as all the patients were catheterized.

Assuming the increase in duration of analgesia to be 8-10 h[3,4] a sample size ≥ 7 would give the study a power of 90% with type I error 0.05. So we conducted this study with 20 patients in each group. A comparison of the mean levels of all variables between two groups was made by the unpaired *t* test. Differences were considered statistically significant if $P < 0.05$.

Results

The study groups were comparable in terms of age, weight, M:F ratio, and duration of surgery [Table 1].

Table 1: Demographic data

	A	B
Number of patients	20	20
Age (years)	38 ± 7	38 ± 8
Weight (kg)	50 ± 10	50 ± 10
Sex ratio (M:F)	6:14	5:15
Duration of surgery (min)	180 ± 30	180 ± 40

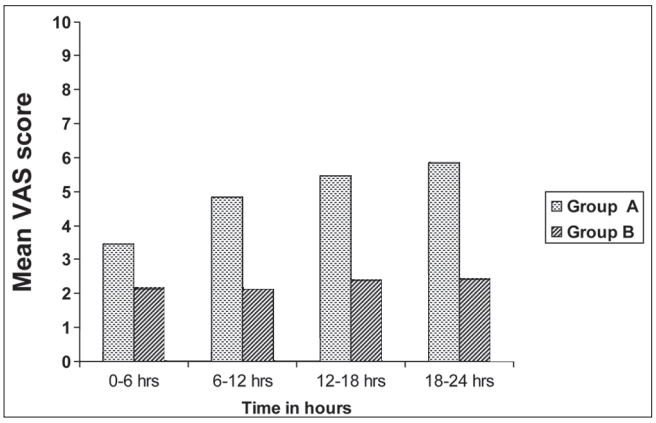

Figure 1: Comparison of mean VAS scores

Mean VAS scores were significantly lower in group B as compared to group A [Figure 1]. In group A, 10% patients required rescue analgesic within 0-6 h, 40% in 6-12 h, 45% in 12-18 h, and 50% of patients in 18-24 h. In group B, 5% patients required analgesia within 0-6 h, 5% in 6-12 h, and 15% in 18-24 hours [Figure 2]. Addition of buprenorphine enhanced the duration of analgesia in group B and the total dose of rescue analgesic used was significantly higher in group A patients [Table 2]. None of the patients had any opioid-related side effects like nausea, vomiting, pruritus, and drowsiness.

Discussion

Post-operative pain arises from the interplay of three factors.

1. Impulses generated from injured nerve fibers innervating the site of incision/retraction/sutures.
2. Inflammatory mediators which are elevated at the surgical site and sensitize uninjured and injured nerve fibers.
3. Sensitization of pain transmitting circuits in the spinal cord which increases their responsiveness to painful and non-painful stimuli.

The trauma of incision, compression, and stretch from surgical retraction induces impulse firing in peripheral neurons. Tissue damage, bleeding, and release of chemo-attractants from injury sites will foster local inflammation. It also stimulates keratinocytes (the predominant cells of skin) which leads to secretion of cytokines and other neuro-active agents causing sensitivity of peripheral tissues and nociception.[5] Blocking of these peripheral nerves innervating the surgical site by local infiltration is a traditional approach for post-operative pain control.

Traditionally, it is believed that opioids exert their analgesic

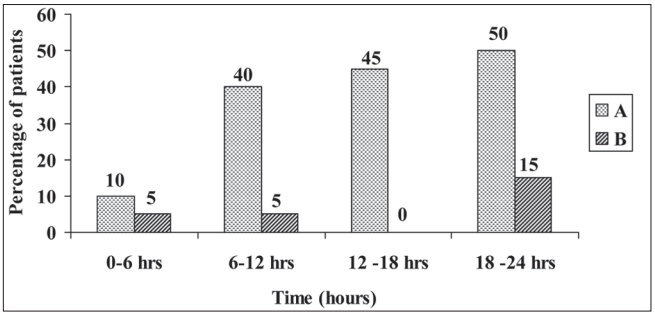

Figure 2: Rescue analgesic requirement (percentage of patients)

Table 2: Rescue analgesic requirement

	Group A	Group B
Time to first analgesic requirement (hours)	3.275 ± 1.8	10.52 ± 5.54*
Total consumption of tramadol in 24 h (mg)	72 ± 12.4	12.5± 5.38*

effect by acting exclusively in the CNS. However, evidence has been mounting that reveals a peripheral opioid action on receptors without central action raising the possibility of divorcing analgesic action from unwanted central side effects. Many clinical studies concerning the analgesic efficacy of peripheral opioids have been published but the results are conflicting and various mechanisms are proposed for activation of opioid receptors on peripheral neurons.[2]

a. Opioids increase potassium current and decrease calcium current in the cell bodies of sensory neurons. This inhibits the neuronal firing and transmitter release as well as the calcium-dependent release of excitatory pro-inflammatory compounds (e.g. substance P) which contributes to their analgesic and anti-inflammatory actions.
b. Opioid anti-nociceptive effect is particularly prominent in inflamed tissue as follows.
    i. Inflammation disrupts the perineurium (normally an impermeable membrane) and facilitates the passage of corticotrophin-releasing hormones (CRH), interleukin 1B, and other cytokines. These substances apparently stimulate the release of opioid peptides from immune cells which activate opioid receptors on the sensory nerve endings leading to anti-nociception.
    ii. Inflammation also enhances the peripherally directed axonal transport of opioid receptors (DRG → periphery) which leads to receptor upregulation (increase in their number in peripheral nerve terminals). Also the previously inactive opioid receptors become active in an inflamed tissue enhancing the analgesic potential of opioids.[2]

This anti-nociceptive effect can further be improved by a concomitant administration of local anesthetic like bupivacaine because they further increase the perineural permeability. Local anesthetics can also inhibit inflammatory and local sensitizing responses by directly suppressing some phases of inflammation like neutrophil priming and by blocking some of the neuronal pathways which are activated by inflammation that is protein kinase C and G protein-coupled receptors.[5]

The physiochemical properties of opioids play an important role in their ability to penetrate axonal myelin and the nerve membrane. We chose buprenorphine as it is a very lipid soluble compound (5 times > morphine) with great analgesic potency, high affinity for μ receptors (50 times > morphine),[6] and relatively long half life. It has an excellent safety profile such as ceiling effect for respiratory depression, lack of immunosuppressive effect, low pharmacokinetic interaction potential, and no accumulation in renal impairment. Moreover, former doubts on antagonism of respiratory effects by naloxone have been disproved and buprenorphine effect can be antagonized with continuous infusion of naloxone. Use of buprenorphine is increasing as it gives a smoother and longer analgesia.[6]

In our study, the mean duration of analgesia was prolonged in the buprenorphine group post-operatively which significantly decreased the requirement of supplemental analgesics. Similar effect was observed by the study of Bazin *et al.* where the duration of analgesia produced by a combination of buprenorphine and a local anesthetic for brachial plexus block was around 20 h.[3] Similarly, Likar *et al.* demonstrated that morphine added to a local anesthetic for submucous infiltration in dental surgery resulted in improved post-operative analgesia up to 24 h.[7] Tverskovy *et al.* also proved that addition of fentanyl for wound infiltration prolonged duration of anesthesia by 50% and decreased the intensity of spontaneous pain.[8] Similar prolongation of post-operative analgesia was seen in the study of Gao *et al.*, who compared a combination of bupivacaine and buprenorphine with bupivacaine alone by caudal blockade for post-operative pain after hip and knee arthroplasty and the mean morphine consumption was halved in the buprenorphine group.[4]

The lack of major side effects was noteworthy. Systemic and spinal administration of buprenorphine for post-operative analgesia is limited by the side effects such as respiratory depression, pruritus, nausea, vomiting, and urinary retention. None of our patients had these side effects.

Conclusion

Adding buprenorphine to local anesthetic can significantly enhance the quality of post-operative analgesia. This peripheral action of opioids particularly in inflamed tissue provides support for the existence of peripheral opioid receptors and gives a new approach to pain management which may have great clinical benefits.

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