Buprenorphine significantly prolongs postoperative analgesia in intravenous regional anesthesia: a double blind randomized clinical trial

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Citation

Abstract

Background: Recently demonstration of opioid receptors along peripheral sensory nerves especially after painful inflammatory conditions forms the basis of peripheral opioid analgesia. This form of opioid antinociception has the potential to help overcome one of the disadvantages of intravenous regional anesthesia (IVRA) that is lack of postoperative analgesia. The aim of the study was to assess the efficacy of Buprenorphine as an adjunct to lidocaine in (IVRA) for postoperative analgesia.
Methods: Seventy-five consenting patients undergoing hand & forearm surgery were randomly allocated into three groups of twenty-five each: group A received 0.5% 40 ml lidocaine for IVRA, group B received 0.5% 40 ml lidocaine for IVRA and Buprenorphine 0.3 mg intramuscularly and group C received 0.5% 40 ml lidocaine with Buprenorphine 0.3 mg for IVRA. Postoperative analgesia was assessed using visual analog scale (VAS) on a 0 to 100 mm scale in the immediate postoperative period and 1 hourly thereafter for 24 hours. Patients were given declofenac 1 mg/kg orally whenever VAS score exceeded 25 or patient demanded analgesic.
Results: Onset time for sensory block was longer in group C as compared to group A & B (5.0±1.0 min versus 4.0±0.6 and 4.0±0.4) whereas motor block onset time was comparable in all the three groups. Quality of sensory & motor block was similar in all the groups. Duration of postoperative analgesia was significantly longer in group C (20 ±2 hrs) as compared to 0.7±0.2 and 7±0.6 hrs for group A & B respectively (p=0.001). Analgesic consumption was also significantly lower in group C (56±9 mg versus 201±27 & 120±24 mg for group A & B respectively (p=0.001). incidence of nausea/vomiting and sedation was much higher in group B as compared to other groups (p=0.002).
Conclusion: We concluded that addition of Buprenorphine 0.3 mg to lidocaine for IVRA significantly prolongs analgesia without causing systemic side effects.

INTRODUCTION

A lot of research work in the field of peripheral opioid analgesia reveals that human peripheral nerves contain opioid ligands as well as opioid receptors & that immune cell produce endogenous opioids during inflammation. These could be the targets for opioids to exert their analgesic effects without causing various side effects when they are given systemically ([1,2,3,4,5]). Intravenous regional anesthesia (IVRA) is a safe, simple to administer, and effective method of providing anesthesia for hand and upper arm surgeries but lack of postoperative analgesia has always been its major disadvantage ([6,7,8,9]). A variety of opioids have been tried so far as adjuncts to local anesthetics for IVRA including fentanyl, sufentanil, morphine, mepridine & tramadol in attempts to improve postoperative analgesia but reports are conflicting ([10,11,12]). Buprenorphine is a synthetic partial μ-

receptor agonist, derived from thebain, one of the opioid alkaloid. It has rapid onset and prolonged duration of action. It is 25-40 times more potent than morphine on parenteral administration. It is potentially safe in conditions of over dosage due to its bell shaped dose response curve and has a low abuse potential. It has been used in brachial plexus and central neuraxial blocks with significant prolongation of postoperative analgesia ([18,19,20,21]). We decided to test the efficacy of buprenorphine along with lidocaine in IVRA for postoperative analgesia in a prospective double-blind study.

METHODS

The prospective randomized double-blind study was carried out in 75 patients scheduled for forearm or hand surgeries like open reduction and internal fixation of both bone forearm, tendon repair and K-wire fixation. The approval of

institutional ethical committee on research and informed consent from patients was obtained. Thorough history, clinical examination and routine investigations including any special investigation, if required were carried out. Patients of either sex, between age group of 18 to 60 years and ASA I and II were included in the study. Patients with known hypersensitivity to local anesthetics, peripheral vascular disease, where use of tourniquet was not possible/contraindicated, sickle cell anemia, diabetes mellitus, cardiovascular diseases like myocardial infarction & cardiac arrhythmias were not included in the study.

Patients were allocated randomly into three groups:-

Group A (control group 1, n=25) - received 40 ml, 0.5% preservative-free lidocaine (Xylocard®, Astrazeneca, India)

Group B (control group 2, n=25) - received 40 ml, 0.5% lidocaine with buprenorphine (Bupregesic®, Neon pharmaceuticals, India) 0.3 mg intramuscularly.

Group C (study group, n=25) - received 40 ml, 0.5% lidocaine with buprenorphine 0.3 mg in IVRA.

The study was kept double blind by one anesthesiologist performing the procedure while other monitoring the patient & recording the duration and quality of analgesia. Duration of analgesia was defined as visual analog scale (VAS) score of more than 25 or time to first analgesic request after deflation of tourniquet.

Intravenous line was secured in contra lateral arm & lactated ringers solution infusion started. A padded double-cuff pneumatic tourniquet was then positioned around the arm, on the side to be operated. A 22G butterfly needle was placed for drug injection in a peripheral vein, preferably over the dorsum of the hand. Now the limb was exsanguinated by elevating it to 90 degrees for three minutes followed by proximal tourniquet cuff inflation to 250 mmHg. Then a dose of 40 ml, 0.5% lidocaine was injected, either alone or with Buprenorphine, depending upon the group, as mentioned earlier. ECG & SpO_2 were monitored continuously. Blood pressure, pulse rate & respiratory rate were recorded preoperatively, immediately after the drug(s) injection and then every 5 minutes.

The time onset of sensory block (by pin-prick) and that of motor block (by finger movement) was then assessed at one minute interval. Similarly time for complete sensory and motor blockade was also noted. After establishment of complete analgesia, distal cuff was inflated to 250 mmHg followed by deflation of proximal cuff. Throughout the procedure tourniquet pressure was monitored. Following completion of surgery tourniquet cuff was deflated with repeated deflation-reinflation technique. For this, cuff was deflated for 10 seconds and then re-inflated again for 1 minute. This sequence was repeated three times. In any case cuff was not deflated within 20 minutes of drug injection & was not kept inflated for more than 1.5 hrs. All the patients were then observed for 2 hrs postoperatively for signs of any untoward reaction. Postoperative analgesia was assessed by anesthesia resident blinded to the study, using VAS scoring at 1 hr interval. Patients were given declofenac 1 mg/kg IM whenever VAS score exceeded 25 & its total consumption in 24 hrs was recorded.

Assessment of quality of block: Sensory blockade was assessed by blunt bevel pin-prick at six areas, representing smaller branches of four peripheral nerves i.e. lateral aspect of forearm for musculocutaneous nerve, dorsal 1st web space for radial nerve, index fingertip and thenar eminence for median nerve and little fingertip & hypothenar eminence for ulnar nerve. Sensory blockade was graded as:

- Excellent- complete anesthesia

- Good- complete anesthesia (touch sensation may be preserved, but not to pin-prick)

- Fair- adequate anesthesia with slight discomfort, tolerable without any supplementation.

- Poor- inadequate anesthesia requiring supplementation either systemic analgesics or general anesthesia with endotracheal intubation.

Motor blockade was assessed by fine finger movement and was graded as:

- Excellent- completely limp.

- Good- minor movement of fingers.

- Fair- weak grip strength.

- Poor- good grip strength and movement of fingers.

Assessment of postoperative pain was done on a Linear Visual Analog Scale (VAS) graded from 0 mm (no pain) to 100 mm (unbearable pain).

Statistical analysis – All data were presented as mean±SD and number of patients. Data were analyzed using StatistiXL version 1.8 for Microsoft Excel 2003. One-way analysis of variance (ANOVA) was employed for analyzing data like onset & duration of analgesia, intra and postoperative analgesic consumption followed by Scheffe's post hoc analysis for multiple comparisons. Kruskal–Wallis test for data like quality of analgesia & VAS scores. Complication rate among groups was assessed using contingency table and ?2 test. P-value of less than 0.05 was considered to be significant.

RESULTS

Demographic data of the groups were similar for mean age, weight, and sex ratio. There was no exclusion from the study because of technical failure. There was no significant difference in duration of surgery and tourniquet time (Table 1).

Figure 1

Table 1: Patient details, times of surgery and tourniquet

Variable	Group A (n=25)	Group B (n=25)	Group C (n=25)
Age (yrs)	45 (32–56)	42 (29–58)	39 (26–54)
Weight (kg)	55.2 ± 3.5	57.2 ± 2.2	56.5 ± 4.4
Gender (m/f)	23/2	24/1	25/0
Operation time (min)	42 ±12	43 ±18	45 ± 23
Tourniquet time (min)	50±9	52±6	60±9

Values are shown as median (range), number of patient or mean ±SD

There was also no difference between groups when compared for mean arterial pressure, heart rate and oxygen saturation (SpO_2) at time in the intra-operative and postoperative period (P>0.05). The onset time for sensory block was longer in group C (5.0±1.0 min) as compared to group A (4.0±0.6 min) & B (4.0±0.4 min) (p=0.001) whereas there was no difference between group A and B (p=0.533). The onset of motor block did not differ between groups (p>0.05). None of the patients suffered from pain on incision in any of the groups and no patient required supplemental analgesic during surgery. The quality of sensory and motor block did not differ between groups when compared statistically (p=0.078 & p=0.088 for sensory and motor block respectively).

Figure 2

Table 2: Sensory and motor block details

Variable	Group A (n=25)	Group B (n=25)	Group C (n=25)
SB onset time(min)	4.0±0.6	4.0±0.4	5.0±1.0
MB onset time (min)	14.0±1.0	14.0±1.0	14.0±2.0
Quality of SB (E/G/F/P)	23/1/1/0	23/2/0/0	25/0/0/0
Quality MB (E/G/F/P)	19/4/2/0	18/4/3/0	20/3/2/0

Values are mean±SD or number of patients. SB = sensory block, MB = motor block. E=excellent, G=good, F=fair, P=poor.

Table 3 shows duration of analgesia and analgesic consumption. In all the patients in group A, analgesic duration did not last for more that 1 hour (0.7±0.1 hrs). In group B mean analgesic duration was 7.0±0.6 hours, majority of patients experienced analgesia between 6 & 8 hours. In group C mean duration of analgesia was 20.0±2.0 hours. Consumption of declofenac was also markedly lower in group C (56.0±9.0 mg) versus 201±27.0 and 120.0±24.0 mg in group A & B respectively (p=0.001).

Figure 3

Table 3: Duration of analgesia and consumption of rescue analgesic in first 24 hrs

Variable	Group A (n=25)	Group B (n=25)	Group C (n=25)	Significance P value
Duration of analgesia (hrs)	0.70±0.2	7.0±0.6	20.0±2.0	0.001
Supplemental analgesic (Declofenac) consumption (mg)	201±27	120±24	56±9	0.001

Values represented as mean±SD

VAS scores after the tourniquet deflation for all the groups are shown in figure1. VAS scores were significantly lower in group B & C as compared to group A (p<0.0001). Similarly there was highly significant difference between group C & B when compared statistically (p<0.0001).

Figure 4

Figure 1: Visual Analog Scale (VAS) values of the groups.
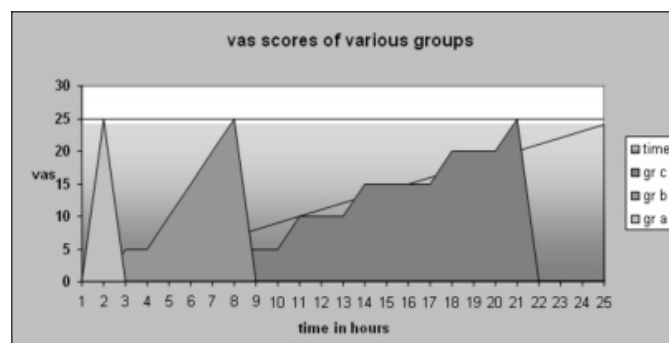
Visual analog scale (VAS) scores of various groups. VAS scores were significantly lower in group C as compared to group A & B (p=0.000). Similarly VAS score in group B were lower in comparison with group A (p=0.000)

All the patients were monitored for 30 minutes postoperatively and then hourly for 24 hrs thereafter for complications, if any. None of the patients in group A experienced any complication in immediate postoperative period and during subsequent 24 hours. Complication rates were significantly higher in group B patients (p=0.002). In group B a total of 18 patients had nausea and vomiting (11/25 & 7/25 respectively) whereas 8 patients had sedation, limited only to drowsiness. In contrast only two patients had single episode of nausea/vomiting while one patient had sedation in group C.

Figure 5

Table 4: Complications in various groups

Complications	Group A (n=25)	Group B (n=25)	Group C (n=25)	Measures taken
Nausea	0/25	11/25	1/25	Inj. Ondansetron 4mg IV
Vomiting	0/25	7/25	1/25	Inj. Ondansetron 4mg IV
Sedation	0/25	8/25	1/25	O2 supplementation & observation
Pruritus	0/25	0/25	0/25	
Respiratory depression	0/25	0/25	0/25	

Values are shown as number of patients.

DISCUSSION

The main finding of our study was that addition of buprenorphine markedly prolongs duration of postoperative analgesia without causing systemic side effects. This was associated with four-fold decrease in analgesic consumption in the study group.

IVRA is a preferred technique for regional anesthesia for upper extremity surgery due to ease of application, safety and low failure rate. Inability to provide effective postoperative analgesia remains major disadvantage of IVRA. Lidocaine 0.5%–1% is one of the commonly used local anesthetic for IVRA [6,7,8,9].

Groups in this study did not differ when compared for demographic and hemodynamic data. Buprenorphine did not have any effect on onset or intensity of tourniquet pain which was not the major concern in our study probably as a result of using double-cuff tourniquet technique. Tsai YC et al compared EMLA cream, subcutaneous ring anesthesia and double cuff technique in the prevention of tourniquet pain and concluded double cuff technique to be most effective [13,14].

In our study addition of buprenorphine to lidocaine in IVRA did not affect onset of motor blockade but slight prolongation of sensory block onset time was observed which is not clinically significant. This finding reported by other workers as well that addition of opioids delays sensory block time [15].

Buprenorphine is a synthetic partial μ-receptor agonist, derived from thebain, one of the opioid alkaloid. It has rapid onset and prolonged duration of action. It is 25-40 times more potent than morphine on parenteral administration. It is potentially safe in conditions of over dosage due to its bell shaped dose response curve and has a low abuse potential [16]. Moreover Yuri A. Kolesnikov, Igor Chereshnev and Gavril W. Pasternak have reported analgesic synergy between buprenorphine and lidocaine [17]. In fact, the duration of the response from the lidocaine/buprenorphine combination exceeded that seen with any of the other opioids tested.

Addition of buprenorphine to lidocaine in IVRA resulted in significant prolongation of analgesia. This was also associated with four fold decrease in analgesic consumption in the postoperative period. Candido KD et al used buprenorphine in brachial plexus block and reported marked

prolongation of analgesia extending up to 30 hours in majority of patients, further endorsing the existence peripheral opioid antinociception ([18]). Similar findings are noted when buprenorphine was added to local anesthetics in central neuraxial blocks ([19,20,21]). Scott S. Reuben et al have reported dose-dependent increase in duration of analgesia with meperidine in IVRA ([22]). Contrary to the traditional view that opioid antinociception takes place exclusively within central nervous system, there are peripheral opioid receptors that mediate analgesia, when activated by exogenous opioid agonists applied in the vicinity. This understanding of the concept of peripheral opioid receptors in sensory afferent neurons have emerged from a series of studies in animals as well humans. Research trial by Christoph Stein reveals small, systemically inactive doses of exogenous opioids administered in the vicinity of peripheral-nerve terminals has beneficial analgesic effects ([4], [5]). This concept has already been exploited in regional anesthesia like brachial plexus blocks with much promise. Such results can also be duplicated in IVRA to alleviate its one of the major disadvantages i.e. lack of postoperative analgesia. To conclude, this study demonstrates that addition of buprenorphine to lidocaine for IVRA significantly prolongs the duration of postoperative analgesia possibly through peripheral mechanism while causing minimal systemic side effects. This finding also correlates with almost four-fold decrease in postoperative analgesic consumption.

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