# Effectiveness of butorphanol as an adjuvant to lidocaine for haematoma or periosteal block: A prospective, randomised, double blind study

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## ABSTRACT

**Background:** The peripheral nerve endings carrying pain contains opiod receptors. Blocking these receptors during haematoma block or periosteal block may provide better analgesia. **Aim:** Evaluation of effectiveness and safety of butorphanol as an adjuvant to lidocaine for haematoma block. **Settings and Design:** This is a two centre, prospective, individually randomised, two group, parallel, double-blind clinical trial. **Methods:** In this study, 115 American society of anaesthesiologist grade I and II adult patients scheduled for closed reduction of fractures were randomly allocated into two groups; Group A received 1% lidocaine (2 mg/kg) where as Group B received 1% lidocaine (2 mg/kg) with butorphanol (0.02 mg/kg) during haematoma block. Pain was assessed before, during and after manipulation of fracture by using visual analogue scale (VAS 0-10). Onset time of block, time for first rescue analgesic, 24 hour analgesic requirement and sedation levels were noted. **Statistical Analysis:** Data analysed with the unpaired *t*-test with Welch correction assuming unequal variances and Fisher's exact test using Graph pad Prism 5.02 version. **Results:** Onset time of haematoma block was significantly less in the butorphanol group compared to the lidocaine group ($P$=0.0003). The mean time for first rescue analgesic was significantly higher and total analgesic requirement was significantly lower in the butorphanol group ($P$<0.0001). Mean VAS scores were lower and sedation scores were higher in the butorphanol group. **Conclusions:** Addition of butorphanol to lidocaine quickens onset of haematoma block, provides excellent post manipulation analgesia and decreases 24 hour total analgesic requirement without excessive sedation.

**Key words:** Butorphanol, closed fracture reduction, haematoma block, periosteal block

## INTRODUCTION

Fracture of a bone is the most painful and distressing event experienced by any person. The best form of pain relief is 'early reduction of fracture'. Various methods of analgesia have been used to alleviate the patient's pain during fracture reduction such as intravenous regional anaesthesia (IVRA), demand-valve nitrous oxide, intramuscular sedation, conscious sedation and general anaesthesia[1] but Haematoma Block is now being frequently used in the Accident and Emergency department for manipulation of distal radial fractures,[2] ankle fractures dislocations[3] and even fracture neck of femur.[4] The increasing popularity of haematoma block over general anaesthesia is due to its safety and effective way to anaesthetise a fracture before manipulation.[5,6]

All of the above procedures are associated with severe post manipulation pain requiring high dose of analgesics. Opiod receptors have been demonstrated in peripheral nerve ending of afferent neurons. Blockade of these receptors by peripherally administered opiod will result in potent analgesia.[7] Hence, we thought

of adding an opiod to local anaesthetic so that it may prolong analgesia of haematoma block. The aim of this study is to evaluate the effectiveness and safety of butorphanol as an adjuvant to lidocaine for haematoma block.

## METHODS

This is a two centre, prospective, individually randomised, two group, parallel and double blind clinical trial carried out from August 2010 to February 2012. After obtaining ethical approval from the ethics committees at both the hospitals, 115 ASA grade I and II adult patients requiring closed manipulation of fractures were consecutively included in the study. Patients were excluded if they refuse to participate; age <16 years; had an open fracture; narcotics, sedatives or any analgesics had been administered after the injury; had an altered mental status, a chest or pulmonary injury; alcohol abuse within 24 hours of injury; history of previous fracture reduction, cardiac or pulmonary disease or allergy to any of the study drug and patients who had block failure. After obtaining written and informed consent, 115 patients were randomised using computer generated, permuted block randomisation with allocation ratio of 1:1 and stratified at centre to receive either 1% lidocaine (2 mg/kg) or 1% lidocaine (2 mg/kg) with butorphanol (0.02 mg/kg) during haematoma blocks. Two senior residents who were not involved in patient care generated random sequence, enrolled participants, assigned participants to interventions, carried out pre-anaesthetic evaluation and prepared randomised study drug mixture. These drug mixtures were provided in sequentially numbered, opaque, sterile sealed envelopes. Haematoma block was performed and parameters recorded by anaesthesiologist blinded to study drug. The patient undergoing haematoma block was also blinded to study drug.

Haematoma block was performed using a conventional technique for radial bone fractures[8] and for ankle fractures[3] which was standardised so that no more than 2 mg/kg of 1% lidocaine (maximum of 200 mg) and 0.02 mg/kg of butorphanol (maximum of 2 mg) was injected into the fracture site. Intravenous access was secured and monitors like pulse oxymetry, non-invasive blood pressure (NIBP) and electrocardiogram were connected. All patients were pre-medicated with injection midazolam 0.03 mg/kg (maximum of 2 mg) I.V. The absolute sterile technique was used during injection. The skin was prepared with 10% Povidone iodine (Betadine) solution and the fracture site entered with a 22 gauge needle. Aspiration of altered blood confirms the presence of a fracture haematoma and needle near the fractured ends of a bone. The average volume of drug injected was 12 ml. After injection of drug, the needle was then removed and a sterile dressing applied. A period of 10 min was left before manipulation.

The following parameters were studied: a) Pain assessment before, during and after reducing the fractures and every two hours thereafter for 24 hours by VAS scores; b) Vital parameters before, during and after manipulation (Pulse rate, Oxygen saturation, Blood Pressure and Electrocardiogram); c) Time of onset of block; d) Time for first rescue analgesic and e) 24 hour analgesic requirement.

After manipulation patients were followed up for duration of analgesia and rescue analgesic was given when patient demands (demand analgesia) or when their VAS scores were more than three. We have given NSAID i.e., Diclofenac sodium 75 mg intramuscular injection as rescue analgesic so that it does not interfere with butorphanol (opiod) and its complications. Patients were observed for development of any complications like nausea, vomiting, sedation, local anaesthetic toxicity and compartment syndrome during the peri-manipulation period. All of them were followed up for any occurrence of osteomyelitis. The Ramsay sedation score[9] was used to assess sedation (1: Anxious or agitated; 2: Co-operative and tranquil; 3: Drowsy but responsive to command; 4: Asleep but responsive to glabellar tap; 5: Asleep with a sluggish response to tactile stimulation; and 6: Asleep and no response).

### Definition of terms
Time of onset of block is defined as 'time required for VAS score to come down to three'.

Block failure or inadequate block is defined as 'VAS scores of four or above after ten minutes of administration of block'.

Excessive sedation is defined as 'Ramsay sedation score of five or more'.

### Statistical analysis
Calculation of sample size was based on the results of our pilot study. This is an internal pilot study where 20 patients randomly allocated to two study groups. The analysis of collected data showed standard

deviation for duration of analgesia of the lidocaine group was 93.5 min and butorphanol was 132.7 min. We assumed target difference in duration of analgesia between groups should be at least 45 min. For the results to be of statistical significance with α=0.05 and β=0.80, one needed to recruit a total of 102 patients or 51 in each group. To increase the power of the study and to compensate for any possible dropouts, we enrolled 115 patients. A comparison of the mean levels of all variables between two groups was made by the unpaired *t*-test with Welch correction assuming unequal variances and categorical data by Fisher's exact test using Graph pad Prism 5.02 version. A two tailed *P* value was calculated and *P*<0.05 was considered to be statistically significant

## RESULTS

During the study period, 115 out of 157 consecutive patients met inclusion criteria and consented for manipulation of fracture under haematoma block. Eleven patients had block failure (inadequate block) and needed general anaesthesia to manipulate fracture, hence excluded from the study [Figure 1]. There were no statistically significant demographic differences between the two groups [Table 1].

Time of onset of haematoma block was significantly less in the butorphanol group than the lidocaine group (*P*=0.0003). The mean time for first rescue analgesic was significantly higher and total analgesic requirement was significantly lower in the butorphanol group (*P*<0.0001). VAS scores were comparable between the groups before, during and immediately after manipulation of fracture, but differ significantly after 2 hours of manipulation. When we observe trend of VAS scores, they were significantly high in the lidocaine group peaking above 5 at 4 hours whereas in the butorphanol group they were well below three up to 12 hour [Figure 2]. We did not encounter any complications except for nausea and sedation. There is no significant difference in incidence of post-manipulation nausea and vomiting between groups (*P*=0.3632) [Table 1]. Ramsay sedation scores were high in the butorphanol group but maximum sedation scores were four [Figure 3].

The overall incidence of haematoma block failure was high (10.57%). Block failure rate was significantly high in lower limb fractures (19.5%) when compared to upper limb fractures (4.05%). The number of patients with ankle fracture was similar in both the groups with 18 patients in the lidocaine group and 15 patients in the butorphanol group. Seven patients out of 58 in
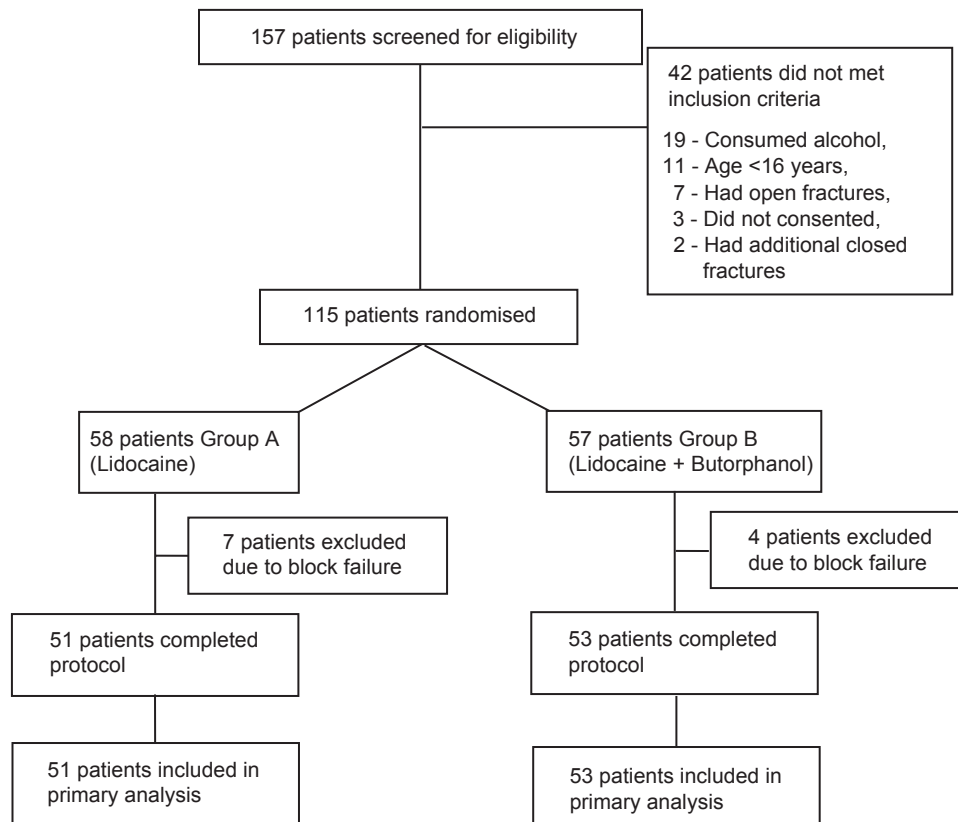
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                ┌─────────────────────────────────────┐
                │ 157 patients screened for eligibility│
                └─────────────────────────────────────┘
                                   │
                                   │        ┌──────────────────────────────┐
                                   │        │ 42 patients did not met      │
                                   │        │ inclusion criteria           │
                                   ├────────┤                              │
                                   │        │ 19 - Consumed alcohol,       │
                                   │        │ 11 - Age <16 years,          │
                                   │        │  7 - Had open fractures,     │
                                   │        │  3 - Did not consented,      │
                                   │        │  2 - Had additional closed   │
                                   │        │      fractures               │
                                   │        └──────────────────────────────┘
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**115 patients randomised**

| 58 patients Group A (Lidocaine) | 57 patients Group B (Lidocaine + Butorphanol) |

| 7 patients excluded due to block failure | 4 patients excluded due to block failure |

| 51 patients completed protocol | 53 patients completed protocol |

| 51 patients included in primary analysis | 53 patients included in primary analysis |

**Figure 1:** Patient flow (according to consort guidelines)

| Table 1: Demographic data and block characteristics | | | |
|---|---|---|---|
| | Group A (lidocaine) | Group B (lidocaine+ butorphanol) | *P* value |
| Number of patients (*n*) | 51 | 53 | |
| Age (yrs) | 56.7±7.5 | 54.5±6.9 | 0.1231 |
| Males/Females | 17/34 | 20/33 | 0.6855 |
| Weight (kg) | 64.3±9.12 | 67±8.9 | 0.1164 |
| Onset time of block (min) | 4.12±1.16 | 3.22±1.31 | 0.0003* |
| First rescue analgesic time (hrs) | 2.41±1.23 | 10.38±1.42 | <0.0001* |
| Total analgesic requirement (mg) | 172.48±19.40 | 66.51±14.62 | <0.0001* |
| PONV | 1 | 4 | 0.3632 |

Data presented as mean±standard deviation except for number of patients and males/females and post-operative nausea and vomiting (PONV), Test done was unpaired t test with Welch correction; Fisher's exact test for male/female ratio and PONV, Yrs – Years; kg - Kilograms; min – Minutes; hrs – Hours; mg – Milligram; * – Statistically significant
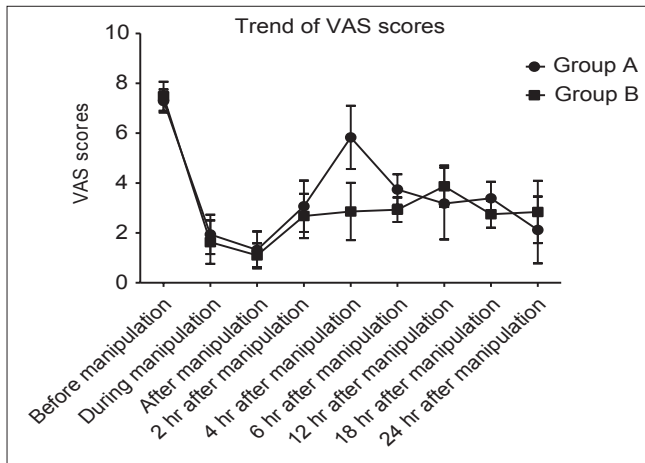


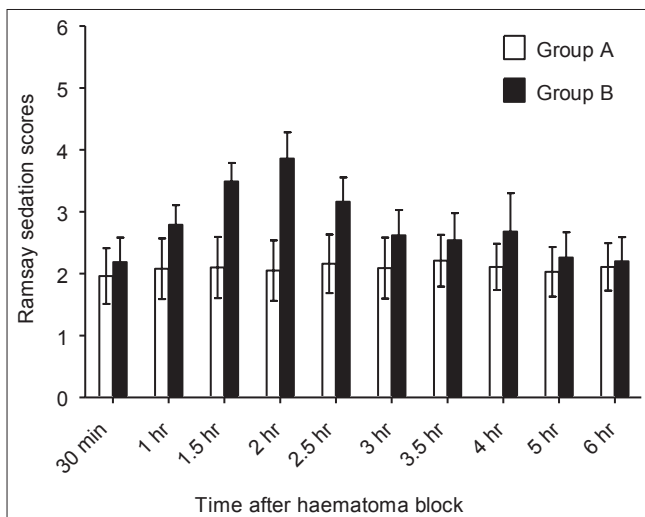**Figure 2:** Visual analogue scale scores in the perimanipulation period



**Figure 3:** Ramsay sedation scores in the post-manipulation period

the lidocaine group and 4 out of 57 in the butorphanol group had block failure but there is no difference in block failure rate between the groups (*P*=0.5281).

## DISCUSSION

Haematoma block is 'the injection of local anaesthetic in to fracture haematoma'.[10] The local anaesthetic targets the nerve fibres, particularly the small, unmyelinated nerves in the periosteum and surrounding tissues, to inhibit the generation and conduction of pain impulses.[11] Hence, it is also called as 'periosteal block'.

Concerns have been raised on safety of haematoma block such as introduction of infection, local anaesthetic toxicity and compression by volume of local anaesthetic leading to compartment syndrome. Basu *et al.* reported a case of osteomyelitis in a 74 year old lady who had fracture reduction under haematoma block. Although the organism isolated was *staphylococcus aureus*, haematogenous spread can be another route of infection in the old lady.[12] The fractured ends of bone will be in close communication with rich venous plexus and manipulation of fracture after injecting drug into haematoma can lead to rapid intravascular absorption of local anaesthetic leading to toxicity. Erik *et al.* reported a case of Lidocaine toxicity following haematoma block where they have used 10 ml of 2% Lidocaine in a 94 year old, 40 kg women. They have used 200 mg of lidocaine which is maximum dose for her; hence, she might have developed toxicity.[13] Meinig *et al.* measured venous plasma levels of lidocaine in eight patients following fracture haematoma block and found that maximum systemic concentrations were seen at 20-30 min and ranged from 100 to 1100 ng/ml which were well below the toxic threshold of 5000 ng/ml.[14] Younge has reported a case of compartment syndrome following haematoma block for wrist fracture.[15]

Six clinical trials involving 531 patients, out of which 317 received haematoma block but none of the above complications were reported.[1,2,16-19] Handoll *et al.* in 2002 reviewed in Cochrane Database of Systemic Reviews regarding anaesthesia for treating distal radial fractures in adults. They included 18 studies involving at least 1200 patients and concluded that 'Considering the risk of intravenous and general anaesthesia, haematoma block is much safer and can be done easily in emergency department'.[20]

During review of literature (PubMed search), we did not find any previous study where adjuvants were used to enhance haematoma block except for London *et al.*,[17] who used hyaluronidase which

did not increase effectiveness of haematoma block. Opioids as an adjuvant to local anaesthetics have been used intrathecally, epidurally and for peripheral nerve bocks. There is lot of evidence for presence of peripheral opiod receptors and their role in alleviation of pain.[7,21] Stein *et al.* and Puhler *et al.* say that opioid receptors are localised on primary afferent neurons carrying pain and the cell bodies of these neurons in dorsal root ganglia express mu-, delta- and kappa-opioid receptor m-RNAs and proteins.[21-23] Opioid receptors are intra-axonally transported into the neuronal processes[24] and they are detectable on peripheral sensory nerve terminals in animals and in humans.[25] Inflammation induces unique simultaneous up-regulation of peripheral opiod receptors and of their endogenous ligands.[26] Mehta *et al.* conducted a study where they infiltrated incisional wound with bupivacaine and buprenorphine and concluded that 'Addition of buprenorphine to the local anaesthetic significantly prolongs post operative analgesia', thus providing evidence in support of the existence of peripheral opioid receptors.[7] Hence, we thought of using opioids for haematoma block.

We choose butorphanol because the analgesic activity is 4-7 times that of morphine, 15-30 times that of pentazocine and has fewer side effects than other opioids and all of them can be reversed by naloxone. The safe dose of butorphanol that can be given intravenously is 20-40 µg/kg.[27] We have used 20 µg/kg of butorphanol in our study. Addition of butorphanol to lidocaine has reduced the onset time of block providing quick relief of pain to patients within three minutes. The duration of post-manipulation analgesia was significantly high up to 11 hours improving the patient satisfaction similar to study conducted by Mehta *et al.* using buprenorphine.[7] The mechanism of action of opioids prolonging analgesia differs from that of local anaesthetics. Local anaesthetics act by blocking the sodium channels at nodes of ranvier where as 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.[28] Hence, the combination of local anaesthetic and opiod has a synergistic effect.

VAS scores were high in the lidocaine group after 2 hours of manipulation, crossing a score of five at 4 hours because the local anaesthetic effect of lidocaine

wears off by 2 to 3 hours. At this time, most of these patients were given rescue analgesic; following which VAS scores came down. In the butorphanol group, VAS scores were well below three for almost 12 hours indicating its action on peripheral opiod receptors after local anaesthetic effect is over. The total analgesic requirement was significantly less in this group and few patients received rescue analgesic.

Another important question is 'whether analgesic effect of Butorphanol is central or peripheral?' Can analgesia be due to its central action after getting absorbed from fracture site? First thing is we are injecting drug into haematoma (blood is stagnant) and diffusion into systemic circulation can occur but slowly. Second is the onset time for haematoma block was reduced indicating local action at the fracture site. Third is the duration of analgesia after intravenous injection of 1 or 2 mg of Butorphanol lasts for 3-5 hours.[27] In our study, the post-manipulation analgesia was 10.38 ± 1.42 hours indicating that action is also peripheral rather than central alone.

Block failure rate was significantly high in fractures of lower limb because

1. Impaction of the fracture prevents the diffusion of the local anaesthetic agent on to the entire periostium
2. Difficulty in localisation of site for injection due to a) body habitus (obese patients); b) traumatic soft tissue swelling; c) Complexity of ankle fractures and
3. Volume of local anaesthetic may not be sufficient enough to block the entire periostium of fractured ends in ankle.

Due to high failure rates (19.5%), haematoma block may not be technique of choice for anaesthetising ankle fractures. To minimise the failure of haematoma block, Biju and Aaron[29] described a technique called circumferential periosteal block so that entire periostium is blocked. Use of ultrasound not only helps to localise the site of injection but also confirms the needle placement between fracture ends, thus improving success rate of haematoma block.[30,31]

Ramsay sedation scores were high in the butorphanol group but maximum score was four and none of patients had excessive sedation. Mild sedation is advantageous for patients after fracture manipulation keeping them calm and comfortable.

## CONCLUSION

We hereby conclude that addition of butorphanol to lidocaine quickens onset of haematoma block, provides excellent post-manipulation analgesia for significantly long time and decreases 24 hour total analgesic requirement without excessive sedation.

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