Tramadol sparing effect of dexmedetomidine as an adjuvant with lignocaine in preoperative stellate ganglion block for postoperative pain relief following upper limb surgeries

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Abstract

Background: Recent literature has established the role of stellate ganglion block (SGB) for management of acute postoperative pain. The effects of dexmedetomidine as an adjuvant to lignocaine in a preoperative SGB for postoperative pain relief have not been evaluated so far.

Methods: The following randomised, double-blinded, control trial included 54 patients scheduled for upper limb orthopaedic surgery under general anaesthesia. Preoperative ultrasound-guided (USG) SGB was performed in all patients. Group I (n = 18) received 3.5 mL of a solution (3 mL 2% lignocaine + 0.5 µg/kg dexmedetomidine for SGB) and 15 mL of intravenous (IV) normal saline (NS). Group II (n = 18) received 3.5 mL of a solution (3 mL 2% lignocaine + 0.5 mL NS for SGB) and 15 mL of IV NS. Group III (n = 18) received 3.5 mL of a solution (3 mL 2% lignocaine + 0.5 mL of NS for SGB) and 0.5 µg/kg dexmedetomidine in 15 mL of IV NS. Postoperatively tramadol consumption and Visual Analogue Scale (VAS) score were recorded up to 48 hours.

Results: The cumulative tramadol consumption at the end of 48 hours (p = 0.01) was significantly reduced in the group I as compared to group II. In group I, postoperative VAS at rest was significantly reduced up to 12 hours postoperatively as compared to group II (p = 0.05). The cumulative tramadol consumption was not reduced significantly in group III compared to group II (p = 0.51).

Conclusion: Dexmedetomidine as an adjuvant to SGB along with lignocaine produced a significant tramadol sparing effect and superior analgesia as compared to IV dexmedetomidine and control group.¹

Keywords

Stellate ganglion block, postoperative pain, tramadol consumption, dexmedetomidine, upper limb surgeries

Introduction

The autonomic nervous system had recently been highlighted in genesis of postoperative pain.¹ In contrast to somatic nerve blocks, selective blockade of sympathetic nervous system for postoperative pain

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relief preserves sensory and motor functions and allows their assessment by surgeons in blocked territory in the immediate postoperative period.²

The earliest confirmation on the role of sympathetic nervous system block for managing postoperative pain was provided by Kumar et al.³ in 2014. However, in that study, the pain scores begin to increase after 8 hours, with concomitant increase in tramadol consumption observed at 12 hours. The results were not known beyond 24 hours. Addition of dexmedetomidine as an adjuvant to local anaesthetics had extended the duration of analgesia and reduced requirement of postoperative analgesics in various nerve blocks.⁴⁻⁹ The effect of dexmedetomidine with lignocaine have not yet been studied on sympathetic ganglion in humans.

According to null hypothesis, we hypothesised that the addition of dexmedetomidine to lignocaine during preoperative stellate ganglion block (SGB) did not have effect on postoperative cumulative tramadol consumption at 48 hours in subjects scheduled for upper limb surgeries under general anaesthesia.

Methods

This prospective, randomised, double-blinded, placebo controlled and single centre clinical trial had an approval from our institutional ethics committee. We presented our data conforming to CONSORT (Figure 1) statement. After written informed consent, subjects ($n=54$) of American Society of Anesthesiologist (ASA; I and II) of either sex, aged between 18 and 60 years, having a body mass index (BMI) of 20–30 kg/m², scheduled for open reduction internal fixation of fracture isolated ulna, isolated radius, both bone forearm, distal end of humerus, fracture distal end of radius with a maximum operative time of 2 hours were enrolled for this study. Exclusion criteria included history of bleeding disorder, substance abuse, local infection, peripheral neuropathy, lactating women, inability to use intravenous patient controlled analgesia (IV PCA) pump, allergy to study drugs or general anaesthesia, acute pain in other region of body and use of chronic pain drugs.

The subjects were randomly allocated into three groups using a computer-generated random number table, and concealment was done with sealed envelopes. The study drug was prepared by an anaesthesiologist not taking part in the study and was not involved in the subsequent assessment of the subjects. Perioperative assessment and recordings of parameters were performed by an anaesthesiologist blinded to the study groups. Subjects were divided into three groups:

- *Group I* ($n=18$). Subjects received preoperative ultrasound guided (USG) SGB with 3.5 mL of a solution (3 mL 2% lignocaine + 0.5 µg/kg dexmedetomidine + normal saline (NS) to make a final

volume of 3.5 mL) and 15 mL of NS by intravenous (IV) route.

- *Group II* ($n=18$). Subjects received preoperative USG SGB with 3.5 mL of a solution (3 mL 2% lignocaine + 0.5 mL NS to make a final volume of 3.5 mL) and 15 mL of NS by IV route.
- *Group III* ($n=18$). Subjects received preoperative USG SGB with 3.5 mL of a solution (3 mL 2% lignocaine + 0.5 mL NS to make a final volume of 3.5 mL) and 0.5 µg/kg dexmedetomidine diluted in 15 mL of NS by IV route.

In the operating room, standard monitoring was used. The cutaneous temperature probe monitored temperature of the hand on the side to be blocked. Sedation scores were assessed before block placement and in the postoperative period by Ramsay Sedation Score.¹⁰

Technique of SGB

In the operating room, SGB was instituted in supine position and neutral position of head. Using standard asepsis, a linear ultrasound transducer high-frequency (5–10 MHz) USG probe (SonoSite®, Inc., Bothell, WA, WA, USA) was used to perform SGB at C7 level using a paratracheal out of plane technique (needle entry between thyroid gland and common carotid artery) with a blunt regional anaesthesia needle 22G, 50 mm (Stimuplex A®; B Braun, Melsung, Germany). The C7 level anatomical landmark was used to facilitate the spread of drug down to C7-T1 which corresponds to the anatomical position of the stellate ganglion.¹¹ The study drugs were injected sub-facially on longus colli muscle after ensuring negative aspiration for blood, cerebrospinal fluid (CSF) or lymph.³

After placement of block, subjects were observed at every 5-minute interval for initial 15 minutes for any inadvertent motor or sensory blockade, change in Visual Analogue Scale (VAS) score (where 0 = *no pain* and 10 = *worst imaginable pain*),¹² rise in temperature of blocked limb from baseline,¹³ features of Horner's syndrome and sedation scores at 5 minutes. During this period, the subjects were administered 15 mL of a solution by IV route as per group allocation and were observed for any other adverse effects such as recurrent laryngeal or phrenic nerve blockade, intravascular injection, development of bradycardia and hypotension. All subjects received general anaesthesia for the procedure. Fentanyl 2 µg/kg and propofol 2–3 mg/kg were administered intravenously at induction followed by vecuronium 0.1 mg/kg to facilitate tracheal intubation. Maintenance of anaesthesia included 60% nitrous oxide in oxygen with 1–2% isoflurane.

Fentanyl 1 µg/kg IV was repeated for surgeries lasting more than 1 hour with maximum dose limited to 3 µg/kg. Approximately, 20 minutes before the completion of surgery, IV tramadol 1 mg/kg was administered. Ondansetron 0.1 mg/kg was administered IV before extubation and every 12 hourly with ranitidine 50 mg IV postoperatively to reduce postoperative nausea vomiting.

At the completion of surgery, residual neuromuscular blockade was reversed with neostigmine 50 µg/kg and glycopyrrolate 10 µg/kg. Each patient received IV paracetamol 1000 mg 6 hourly, diclofenac 75 mg 12 hourly and IV tramadol PCA (Master PCA pump®; Fresenius Vial, Breznis, France) in the postoperative period. IV PCA incorporated individual boluses of 2 mL of tramadol (10 mg/mL)¹ with lockout interval of 20 minutes between two boluses.^{14,15} The maximum dose of tramadol was restricted to 400 mg in 24 hours.¹⁶ Subjects requiring more than 400 mg tramadol were switched to other analgesics and were managed as intent to treat.

All subjects were monitored in post anaesthesia care unit (PACU) and later in ward for the following parameters:

- Haemodynamics (pulse rate (PR) and blood pressure);
- Respiratory rate;
- Pain intensity by VAS at rest and VAS at movement;
- Complications of opioids nausea or vomiting by Categorical scale¹⁷ (where 0 = none, 1 = mild, 2 = moderate, 3 = severe), shivering, pruritus and sedation by Ramsay Sedation Score (1–6, Table 1);¹⁰
- Tramadol consumption;
- Subjects satisfaction was assessed at 24 and 48 hours using a satisfaction score of 5–1 postoperatively (where 5 = very satisfied, 4 = satisfied, 3 = undecided, 2 = dissatisfied, 1 = very dissatisfied);
- Most subjects received splint postoperatively, whereas casts were provided to patients with distal end humerus surgeries.

The above-mentioned observations were done at the following time intervals 0, 2, 4, 6, 8, 12, 24, 36 and at 48 hours postoperatively. Decoding was done at the completion of study.

Sample size calculation and statistical analysis

The sample size was calculated from few pilot cases data in our hospital where a mean tramadol consumption was estimated between subjects receiving

Table 1. Ramsay¹⁰ Sedation Score.

Score	Description
<i>If awake</i>	
1	Anxious, agitated, restless
2	Cooperative, oriented, tranquil
3	Responsive to commands only
<i>If asleep</i>	
4	Brisk response to light glabellar tap or loud auditory stimulus
5	Sluggish response to light glabellar tap or loud auditory stimulus
6	No response to light glabellar tap or loud auditory stimulus

dexmedetomidine with lignocaine in SGB along with IV saline and only lignocaine in SGB with IV saline for postoperative pain relief in patients undergoing upper limb surgeries. To ensure a 10% difference in tramadol consumption with beta error of 0.20 (i.e. power of 80%) and alpha error of 0.05, the sample size was calculated with 15 patients per group. However, adjusting a dropout rate of 20%, a final sample size was estimated with 18 patients per group with a confidence interval of 95%.

Mean and medians were calculated for all quantitative variables i.e. PR, mean arterial pressure (MAP) and for measures of dispersion (standard deviation and standard error). For normally distributed data, means were compared using independent sample t-test. For skewed data, Mann–Whitney test were applied. For time related variables, repeated measure (analysis of variance (ANOVA)) was applied. Qualitative (i.e. ASA grade < 2, BMI < 30) or categorical variables were described as frequencies and proportions. Proportions were compared using chi-square or Fisher's exact test whichever were applicable. Bonferroni-correction was applied for all time dependent variables between the groups. All statistical tests were two-sided and were performed at a significance level of $p \leq 0.05$.

Results

In total, 54 subjects completed the study (Figure 1). The demographic details of all the groups were comparable ($p > 0.05$; Table 2). The mean tramadol consumption at the end of 48 hours (56.67 ± 21.96 ; 81.11 ± 26.09 ; 70.00 ± 24.01) were observed in groups I, II and III, respectively. The total tramadol consumption at the end of 48 hours was higher in group II as compared to groups I and III, but a significant value was observed only between groups I and II ($p = 0.01$; Figure 2). The hourly tramadol consumption was

Figure 1. CONSORT flow diagram.

Table 2. Comparison of patient characteristics in the three groups.

Characteristic	Group I (n = 18)	Group II (n = 18)	Group III (n = 18)	p value
Age (years), mean $\pm$ SD	31.61 $\pm$ 10.70	33.61 $\pm$ 11.39	31.39 $\pm$ 11.93	0.81
Sex				
Males	16 [88.9%]	12 [66.7%]	14 [77.8%]	0.27
Females	2 [11.1%]	6 [33.3%]	4 [22.2%]	
Weight (kg), mean $\pm$ SD	66.44 $\pm$ 10.72	65.89 $\pm$ 15.26	63.39 $\pm$ 12.85	0.76
BMI (kg/m ²), mean $\pm$ SD	26.14 $\pm$ 2.41	26.13 $\pm$ 2.99	25.05 $\pm$ 2.64	0.39
ASA (Category I)	18 [100%]	17 [94.4%]	16 [88.9%]	0.34
ASA (Category II)	0 [0%]	1 [5.6%]	2 [11.1%]	

SD: standard deviation; BMI: body mass index; ASA: American Society of Anesthesiologist.

Group I: Lignocaine and dexmedetomidine in SGB; group II: control group (lignocaine in SGB); group III: lignocaine in SGB with IV dexmedetomidine.

found to be significant only at 4 hours postoperatively ($p=0.01$; Figure 3) between groups I and II. No significant difference was observed on comparing groups II and III.

The VAS at rest was significantly reduced at 2, 4, 6, 8 and 12 hours postoperatively ($p=0.02, 0.01, 0.00, 0.01, 0.04$) in group I compared to group II (Figure 4). The postoperative VAS at rest was significantly reduced only at 6 hours in the group III as compared to group II ($p=0.02$; Figure 5). The postoperative VAS on movement was significantly reduced at 8 hours in the group I ($p=0.03$) compared to group II (Table 3). No

significant difference was observed in VAS at movement between group II and group III.

The mean temperature gain in Celsius were 2.03 ± 0.98 , 2.66 ± 1.62 and 1.89 ± 1.3 in groups I, II and III, respectively, and were statistically insignificant. The maximum rise in temperature was seen at 10 minutes in all the three groups.

Regarding Horner's syndrome, there was variability in the development of different features of Horner's syndrome in all the three groups. Chemosis in groups I, II and III were 61.1%, 66.7% and 61.1%; meiosis 33.3%, 38.9% and 44.4%; and ptosis 22.2%, 33.3% and 55.6%, respectively, were statistically insignificant among the groups.

None of our subjects reported of any complications associated with SGB. The haemodynamic parameters were within normal physiological range for all time intervals in the three groups. None of the subjects had nausea, vomiting, pruritus, shivering and sedation, and postoperative satisfaction scores did not have any significant difference.

Discussion

Acute injury leads to activation of sympathetic nervous system and augmentation of nociceptive transmission before surgery.¹⁸ Surgical manipulation produces local and systemic inflammatory mediators which further add to nociceptive stimuli via neuroendocrine mechanisms.¹⁹

Methods employed to treat the inflammatory and sympathetic components include administration of systemic opioids, nonsteroidal anti-inflammatory

Figure 2. Total tramadol consumption at the end of 48 hours in the groups.

Group I: Lignocaine and dexmedetomidine in SGB; group II: control group (lignocaine in SGB); group III: lignocaine in SGB with IV dexmedetomidine.

*Significant p value.

Figure 3. Postoperative comparison of tramadol consumption.

Group I: Lignocaine and dexmedetomidine in SGB; group II: control group (lignocaine in SGB).

*Significant p value.

Figure 4. Postoperative comparison of visual analogue score (VAS) at rest between group I and group II. Group I: Lignocaine and dexmedetomidine in SGB; group II: control group (lignocaine in SGB). *Significant p value.

Figure 5. Postoperative comparison of visual analogue score (VAS) at rest between group II and group III. Group II: Control group (lignocaine in SGB); group III: lignocaine in SGB with IV dexmedetomidine. *Significant p value.

drugs (NSAIDs) and peripheral nerve blocks (PNBs).¹ PNBs alter motor, sensory and autonomic functions and produce difficulty in surgeon's assessment of motor and sensory functions in the immediate postoperative period as well as delay rehabilitation in early postoperative period.² Hence, selective blockade of sympathetic nervous system offered a ray of hope in providing analgesia and preserving motor and sensory function in the early postoperative period. The results were available only for 24 hours. This study provides an insight into pain intensity, analgesic requirements and the role of dexmedetomidine as an adjuvant for up to 48 hours postoperatively after SGB.

We observed a significant reduction in the total tramadol consumption at the end of 48 hours in group

Table 3. Postoperative comparison of visual analogue score (VAS) on movement.

Time (hours)	Group I (n=18)	Group II (n=18)	p value
0	6 [2-8]	6 [3-8]	0.27
2	5 [2-7]	5 [3-7]	0.31
4	5 [2-7]	5 [3-7]	0.31
6	3 [0-6]	4 [2-6]	0.06
8	3 [0-5]	4 [2-6]	0.03
12	2 [0-4]	3 [1-5]	1.00
24	2 [0-4]	2 [0-5]	1.00
36	2 [0-4]	2 [0-4]	1.00
48	2 [0-3]	1 [0-3]	1.00

Data are shown as mean (range).

Group I: Lignocaine and dexmedetomidine in SGB; group II: control group (lignocaine in SGB).

I as compared to control group (group II), thus rejecting the null hypothesis. However, the difference in tramadol consumption between group III and group II was statistically insignificant. The decreased tramadol consumption in both the groups possibly indicates a role of dexmedetomidine in enhancing the effects of a preoperative SGB.

The postoperative tramadol consumption of group II in this study (80.0 ± 27.4) was comparable with lignocaine group of Kumar et al.³ (97.3 ± 16.6), at 24 hours postoperatively. Addition of dexmedetomidine as an adjuvant in this study further reduced the total tramadol consumption in group II (56.7 ± 21.9) as well as in group III (70.0 ± 24.0) at 24 hours postoperatively. In contrast to Kumar et al.,³ tramadol consumption did not increase from 8 to 12 hours postoperatively in the lignocaine group probably due to additional analgesic effects of paracetamol and diclofenac administered at 6 hours postoperatively.²⁰ The continued consumption of tramadol observed in the group II up to 36 hours as compared to group I in this study indicates enhanced pain relief in group I. The reduction in tramadol consumption observed after 12–24 hours postoperatively in the study of Kumar et al.³ was also seen in this study.

In this study, significant reduction in VAS at rest up to 12 hours postoperatively in group I as compared to group II was observed. On comparing VAS scores to the study of Kumar et al.,³ we did not find an increase in VAS at rest after 8 hours indicating that dexmedetomidine as an adjuvant, prolonged the duration of SGB, which is cited in the literature as 7–12 hours.²¹ The extended 4 hours (from 8 to 12 hours) duration of pain relief in dexmedetomidine in this study also corresponds to an increase in mean duration of motor and sensory block by 4–5 hours in other studies.^{6–8} In contrast to Kumar et al., a significant reduction in VAS at movement observed at 8 hours in our study could be

attributed to an additional analgesic effect of dexmedetomidine persisting during ambulation. For the IV group, the pain relief and tramadol consumption did not reach statistical significance when compared to group II.

Dexmedetomidine has dual mechanisms of action as an adjuvant on perineural application. First, it blocks pain transmission in A δ and C fibres²² and prevents regaining of resting potential by nerves from a hyperpolarised state²³ with a mechanism similar to clonidine.²⁴ Second, in animal studies, perineural dexmedetomidine also prolonged the duration of vasodilatation produced by SGB in the ipsilateral limb²⁵ and facilitated wash out of mediators of pain from the blocked limb.²

Choi et al.²⁶ questioned the effectiveness of SGB as mono-therapy for management of acute postoperative pain relief but with a different study design and did not distinguish measured pain scores at rest or on movement. The use of multiple analgesic drugs (fentanyl, ketorolac and tramadol) for postoperative pain could have resulted in reduced VAS scores in control group also. Moreover, use of adrenaline in the irrigating fluid used for arthroscopic surgeries could have attenuated the vasodilatory effects of the SGB.²⁷

In this study, the reduced consumption of tramadol observed in group III failed to reach statistical significance when compared to the control group and gains support from findings of Marhofer et al.⁷ where authors suggested a direct effect of intravenously administered dexmedetomidine on the central nervous system in subjects with ulnar nerve block.

This study received support from a study by Abdallah et al.,²⁸ where total analgesic consumption at 24 hours was similar in both the IV (dexmedetomidine 0.5 μ g/kg) and control group. In contrast, Kathuria et al.²⁹ demonstrated a significantly decreased analgesic consumption when comparing such groups due to difference in study design where higher the dose of dexmedetomidine (50 μ g) IV was used and postoperative supplemental analgesia was not described.

The significant reduction in VAS up to 12 hours postoperatively in group I could be attributed to additional effect of perineural dexmedetomidine described above and supports findings of Das et al.³⁰ and Almarakbi and Kaki.³¹

The difference in VAS scores between group III and group II in this study was significant only at 6 hours postoperatively, whereas insignificant lower VAS scores in group III as compared to group II present at all time points. This could be attributed to the waning effect of drugs used for general anaesthesia by 4 hours, whereas the analgesic effects of IV dexmedetomidine still persisted in group III compared to control group. After 6 hours, the analgesic effect of dexmedetomidine in group III also diminished due to completion of four to

five half lives of dexmedetomidine: one half life is 2–3 hours.³²

The significantly lower postoperative mean VAS on movement in the group I at 8 hours could be related to dual action of dexmedetomidine on neural tissue and to the waning effect of general anaesthesia in both the groups and corresponding to the time of patient ambulation and physiotherapy. Moreover, stimulation of already sensitised dormant and functional receptors on movement leads to increased pain.³

The insignificant postoperative VAS on movement demonstrated by Kumar et al.³ in between the groups further strengthens the contribution of dexmedetomidine in the analgesic effects of a SGB in this study.

The development of Horner's syndrome is subjective and may not be present in some of the subjects.³³ The SGB given at C7 level along with the low volume of local anaesthetic used in this study prevented spread of the drug more cranially.² Therefore, all patients did not develop all features of Horner's syndrome.^{34,35}

The rise in temperature in the blocked limb (an indicator of successful block) in this study was insignificant in all groups and corresponded to a temperature rise of (1.99 ± 1.23) observed in a study where SGB was instituted to subjects of complex regional pain syndrome (CRPS).³⁶

This study obtains its strength from its novelty in highlighting the first use of dexmedetomidine as an adjuvant to lignocaine in SGB for managing postoperative pain. Although the vasodilatory effects of dexmedetomidine have been studied in animals, the effect of dexmedetomidine on sympathetic ganglion has still not been studied on humans for pain relief.

The limitations include the applicability of results only in ASA grade I and II subjects and the findings cannot be extrapolated to higher grades of ASA and outside the age group of 18–60 years. Most subjects ambulated at 12 hours postoperatively, but information relating to long-term functional outcome, resumption of daily life activities and complications could not be studied. The effect of preoperative SGB on postoperative pain relief in non traumatic orthopaedic surgeries or in subjects outside the exclusion criteria needs further evaluation.

In conclusion, addition of dexmedetomidine as an adjuvant to lignocaine in SGB for managing postoperative pain in ASA I and II subjects after upper limb orthopaedic surgery exhibited significant tramadol sparing without any significant adverse events.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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