INTRODUCTION

Preference to neuraxial anaesthesia has been an emerging trend especially in lower limb orthopaedic surgeries due to its benefits over general anaesthesia including safety, reliability and reduced adverse effects leading to shortened stay in the hospital.\(^1\) Furthermore, with the increasing awareness that postoperative analgesia plays an important role in the better postoperative outcomes of patients,\(^2\) there is emphasis on the techniques having beneficial effect on the pain score resulting in decreased rescue analgesic requirement in the postoperative period.

In this context, encouraging results have been observed using neuraxial adjuvants\(^3,4\) in decreasing the rescue analgesic requirement as compared to intravenous analgesics. Neuraxial adjuvants improve postoperative analgesia and may reduce the need for rescue analgesics during the postoperative period.\(^5\) The efficacy of intravenous versus intrathecal adjuvants is not well established.

METHODS

Ninety patients, aged 20–60 years belonging to American Society of Anaesthesiologists (ASA) physical status I and II, scheduled for below knee orthopaedic surgeries under subarachnoid block were enrolled. In group I \((n=45)\) patients received intravenous dexmedetomidine 0.5 \(\mu\)g/kg in 100 mL 0.9% normal saline [NS] intravenous over a period of 15 minutes given 20 minutes before SAB. Subarachnoid block was given with intrathecal (IT) 0.5% bupivacaine (H) 12.5 mg (2.5 mL) with 0.3 mL of NS. Patients in group II \((n=45)\) received 100 mL of 0.9% NS over a period of 15 minutes given 20 minutes before subarachnoid block. SAB was given with intrathecal 0.5% heavy bupivacaine 12.5 mg with 3 \(\mu\)g of dexmedetomidine (0.3 mL). The primary outcome was duration of analgesia and rescue analgesic requirement, whereas secondary outcome included pain scores.

RESULTS

The duration of analgesia was prolonged in group II (median [IQR]: 5 (6–7.5) h than in group I (median[IQR]: 4[2–4.5] h, \(P=0.000\)). Median dose of rescue analgesics over period of 24 hours was less in group II as compared to group I (median [IQR]:150 (75–150) mg vs 195 (150–225) mg, \(P=0.000\)). VAS score was lower in group II till 12 h in the postoperative period \((P=0.00)\). Conclusion: Intrathecal dexmedetomidine is more efficacious as compared to intravenous dexmedetomidine, due to favourable outcomes in terms of increased duration of postoperative analgesia and reduced rescue analgesic requirement.

Key words: Adjuvant, analgesia, dexmedetomidine, subarachnoid block
to local anaesthetic (LA) agents alone. The dexmedetomidine, α2 receptor agonist, as adjuvant to intrathecal LA has been proved to be beneficial in prolonging postoperative analgesia.[5,6] Similarly, dexmedetomidine via intravenous route as adjuvant in subarachnoid block results in prolonged duration of analgesia and decreased rescue analgesic requirement in the postoperative period.[7]

In a previous study,[8] authors have compared the efficacy of IV (0.5 μg/kg) vs IT (3μg) dexmedetomidine as adjuvant to IT bupivacaine and a significant prolongation in the durations of motor and sensory block was observed.

We hypothesised that intravenous dexmedetomidine as adjuvant in SAB might have analgesic efficacy comparable to intrathecal dexmedetomidine. Therefore, we compared the analgesic efficacy of dexmedetomidine via either intravenous or intrathecal route as adjuvant to bupivacaine 0.5% (H) in patients scheduled for lower limb orthopaedic surgeries under subarachnoid block.

**METHODS**

After approval by the Institutional Ethics Committee and written informed consent, 90 American Society of Anaesthesiologists (ASA) I–II patients in the age group 20–60 years, scheduled for below knee orthopaedic surgery under SAB were enrolled in a randomised, and double blinded study over a period of 12 months. The trial is registered with the Clinical Trial Registry-India (CTRI) (trial registry number: 2017/08/09546). The patients were excluded from the study on the basis of patient refusal, allergy to the study drugs, absolute contraindication for spinal anaesthesia, body mass index >30 Kg/m² and patients noted to have dysrhythmias on the electrocardiogram (ECG).

On arrival to the operating room, standard anaesthesia monitors were attached to the patient including electrocardiogram, non-invasive blood pressure cuff and pulse oximeter, and baseline parameters were recorded. An intravenous line (IV) was secured and preloading was done with normal saline [NS] solution (15 mL/kg). The study drug was administered intravenously over a period of 15 minutes, starting approximately 20 minutes prior to instituting SAB. Following the drug administration, under all aseptic conditions the SAB was performed in the sitting position at the L3–L4 level through a midline approach using a 26-G Quincke spinal needle (B. Braun Medical, USA). Using a computer-generated random list, patients were assigned to one of the two groups: In group I (n = 45) patients received intravenous (IV) dexmedetomidine 0.5 μg/kg in 100 mL of 0.9% NS over a period of 15 minutes given 20 minutes before subarachnoid block. SAB was instituted using intrathecal (IT) 0.5% heavy bupivacaine 12.5 mg (2.5 mL) with 0.3 mL of NS. Whereas, group II (n = 45) patients received 100 mL 0.9% normal saline IV over a period of 15 minutes given 20 minutes before subarachnoid block. Subarachnoid block was instituted using 0.5% bupivacaine (H) 12.5 mg with 3μg of dexmedetomidine (0.3 mL) in sitting position. Immediately after spinal injection, all patients were turned into the supine position. Investigator assessing and recording intraoperative and postoperative parameters was blind to patient group allocation.

After placing the patient in supine position, the sensory level was assessed by pinprick sensation using a blunt 25-G needle along the mid-clavicular line bilaterally at 3, 6, 9, 12, 15, 20, 25 and 30 min. The time to reach the sensory level up to T10 dermatome and the time for regression to S1 segment was recorded. Duration of analgesia was taken as time interval between onset of sensory blockade and first dose of rescue analgesic given to the patient.

All patients were administered oxygen through oxygen mask @ 4 litres per min and monitored intra operatively for systolic, diastolic, mean blood pressure, heart rate, oxygen saturation and respiratory rate every 1 min for first 10 min and then every 3 min for half an hour and then every 5 min till the end of surgery in operating room and 15 min in recovery room. Any hypotension (SBP <90 mmHg) episode was treated with injection mephenetermine 3 mg bolus and episodes of bradycardia (HR <40 beats/min) with intravenous atropine 0.02 mg/kg. The level of sedation was recorded on the scale of 1 to 6 utilising Ramsay Sedation Score [RSS].

The pain scores of the patients were assessed using a 10 point visual analogue scale (VAS) for 24 h in the postoperative period, at hourly interval for next 6 h after subarachnoid block and then at 8th, 10th, 12th, 15th, 18th and 24th h. The postoperative rescue analgesia was provided by diclofenac sodium 1.5 mg/kg slow infusion (VAS >3), and if not relieved within 30 min then intravenous tramadol (1 mg/kg) was to be given. The time to request for first rescue analgesia...
(pain free interval), frequency of rescue analgesia required and total dose of diclofenac and tramadol was noted. Patients having inadequate analgesia requiring IV analgesics or general anaesthesia were excluded from the study.

Statistical analysis
The sample size was based on a previous study, considering primary outcome as duration of postoperative analgesia. To detect the difference of 130 min between two groups, with a level of significance of 0.05 and power of 80%, a sample size of 42 patients per group was required. Therefore, we recruited ninety patients in our study keeping in view the probability of dropouts and block failure.

For statistical analysis SPSS software 17 (SPSS Inc., Chicago, IL, USA) was used. The one-sample Kolmogorov–Smirnov test was employed to determine whether data sets differed from a normal distribution. Uniform data was analysed by unpaired t test, whereas non-normally distributed data was analysed using Mann–Whitney U test. For categorical data, Chi-square (χ²) test was used. We calculated and compared the need of rescue analgesic at various time intervals in two groups utilizing Kaplan–Meier analysis. Probability value (P value) less than 0.05 was considered as significant in all the tests applied.

RESULTS
Ninety patients were randomised into two groups, however, one patient was excluded from the study because of conversion to general anaesthesia in group II. Thereby remaining eighty nine, forty five in group I and forty four in group II completed the study successfully [Figure 1].

Patients in the two groups were comparable with regard to age, gender, BMI, ASA Physical Status and the duration of surgery [Table 1]. Comparable time (P = 0.839) was required for sensory block to reach at T₁₀ level in group II with median (IQR) of 3 (2–6) and in group I 3 (2–5) minutes.

The median duration of sensory block taken as the time from intrathecal injection to regression of the sensory block to S1 level was more in group II 5 (5.5–7 h) than in group I with median (IQR) of 4 (2–4) h (P = 0.000).

The time to request for first rescue analgesia (diclofenac) was prolonged in group II median [IQR]: 5 (6–7.5) h than in group I (median[IQR]: 4[2–4.5] h, P = 0.000) [Figure 2].

Median dose of diclofenac consumption over a period of 24 h was less in group II as compared to group I (median [IQR]: 150[75–150] mg vs 195[150–225]mg, P = 0.000) respectively. [Figure 3] The Kaplan–Meier curve was used to generate a display of time to rescue analgesic among two groups. The intravenous group required rescue analgesic from 2 h up to 6 h with maximum boluses usage at 2 h, 4h and 5 h. Whereas, in intrathecal group the rescue analgesic requirement started from 6 h onwards and extended till 10 h. Maximum doses were required at 6 and 7 h. None of the patients required the second rescue analgesic in either group [Figure 4].

VAS score was less in the group II beyond 2nd h to 12 h as compared to group I in the postoperative period (P < 0.00) and thereafter comparable to group I patients [Figure 5]. Intra-operatively 15 patients had mild sedation with Ramsay Sedation Score 2 in Group I (33% vs 0%). Moreover, beyond 3 h of surgery, none of the patients had sedation. The intraoperative vitals were stable and comparable in both groups.

DISCUSSION
The efficacy and safety of intrathecal dexmedetomidine as adjuvant to local anaesthetic has been the topic of debate for years. In the study done by Yektas et al., the patients undergoing surgeries under subarachnoid block with dexmedetomidine as adjuvant to intrathecal bupivacaine, were assessed for neurological parameters utilising magnetic resonance imaging (MRI) scanning. The authors observed normal study of lumbar and thoracic spine during patient’s yearly neurological examinations. There were no radiculopathy findings in lower extremities of patients in the electromyographic (EMG) studies, ensuring safety of intrathecal dexmedetomidine.
However in another research article,[9] the authors are of the opinion that although dexmedetomidine is a good and safe LA adjuvant there is insufficient safety data to support the use of neuraxial dexmedetomidine in the clinical setting.

Recently in a study,[10] a total of 50 patients scheduled for elective perianal surgeries were randomly allocated to groups C or D (n = 25). Group D received hyperbaric bupivacaine 0.5% (4 mg) + dexmedetomidine 5 µg and group C received hyperbaric bupivacaine 0.5% (4 mg) + dexmedetomidine 3 µg intrathecally. The authors concluded that the duration of analgesia was comparable in two groups D and C (337.86 ± 105.11 min vs 340.78 ± 101.81 min), respectively. The postoperative pain scores were also comparable amongst two groups. Therefore, dexmedetomidine in the dose of 3 µg seems to be a safer choice as intrathecal adjuvant to local anaesthetic.

The potential role of intravenous dexmedetomidine either as bolus or infusion in neuraxial anaesthesia has been evaluated in few studies[11] and it has been observed that it prolongs the sensory-motor blockade and provides better perioperative analgesia extending well into postoperative period. Jaakola et al.[12] in an evaluation of the analgesic efficacy of different doses of intravenous dexmedetomidine (0.25, 0.5 and 1 µg/kg) on ischemic pain in healthy volunteers demonstrated that moderate analgesia was observed with a ceiling effect at 0.5 µg/kg.

Lee et al.[13] using two different doses of dexmedetomidine 0.5 µg/kg and 1 µg/kg IV bolus as
observed that use of intravenous dexmedetomidine resulted in 61% reduction in pain score at 6 h and 53% prolongation of the time of first analgesic request as adjuvant to SAB. However, rapid intravenous administration of dexmedetomidine results in sudden hypotension and bradycardia until the central sympatholytic effects dominates. With this in mind, dexmedetomidine was given in the dose of 0.5µg/kg over 15 min in the study.

The duration of analgesia or time to rescue analgesia was the time at which patient requested first analgesic. The duration of analgesia was less in group I [median (IQR): 4 (2–4.5) h] as compared to group II [5 (6–7.5) h]. Our results are comparable to study, concluding that both intrathecal and intravenous dexmedetomidine were safe adjuvants to bupivacaine during spinal anaesthesia in knee arthroscopies, however the intrathecal route provided more stable haemodynamics, better postoperative analgesia and lesser overall side effects.

Similar results were observed by Hamed and colleagues in relation to the duration of analgesia. The duration of postoperative analgesia was more in intrathecal group [mean ± SD: 5.40 ± 1.25h] in comparison to intravenous group [3.29 ± 0.85h]. However, contradictory results were observed in a study, with the requirement of first rescue analgesic significantly earlier in intrathecal dexmedetomidine group as compared to intravenous group (270.15 ± 25.00 vs 371.25 ± 88.54 min). In this study, the intravenous dexmedetomidine was given as loading dose [1 µg/kg] followed by maintenance infusion [0.4 µg/kg/h] throughout the study interval.

Whereas, in another study, despite the fact that the dexmedetomidine was given as infusion [1 µg/kg] followed by maintenance [0.25 µg/kg] in the intraoperative period following subarachnoid block, the mean time of first analgesia required was significantly more in group IT (8 ± 1 h) as compared to 5 ± 1 h in group IV.

With regard to total dose of rescue analgesic in our study, the patients in group IT required less rescue analgesic as compared to group IV. However in a previous study, the consumption of rescue analgesic was comparable in the dexmedetomidine IV and IT group. In the above mentioned study, the IV dexmedetomidine bolus [0.5µg/kg] was given after...
the subarachnoid block in comparison to our study with IV dexmedetomidine given prior to institution of subarachnoid block.

We observed comparable VAS scores in both groups till 2 h, and thereafter the VAS scores were less in IT group as compared to IV group. However, in the study\(^{(19)}\) comparing IV vs IT dexmedetomidine as adjuvant to bupivacaine in parturients undergoing caesarean section, the authors observed comparable VAS scores in two groups over a period of 24 h. The parturients received dexmedetomidine infusion at the rate of 0.5 µg/kg/h after the institution of SAB in the study as compared to our study.

In our study, 15 patients had mild sedation [Ramsay Sedation Score 2] in group I vs II (33% vs 0%).

However, in the previous study,\(^{(16)}\) the authors observed significantly higher sedation score in group B (IV) of average 2.54 compared to group A (IT) score of 2.25. The higher sedation score in both groups may be attributed to 5 µg intrathecal dexmedetomidine as compared to 3 µg in our study, and the intravenous single bolus of dexmedetomidine in our study was given prior to subarachnoid block as compared to post spinal in the above mentioned study.

The limitation of the study is that only ASA I and II patients were enrolled and the effect in ASA III and IV patients is of concern particularly with regards to cardiovascular co morbidities. The second limitation being study not sufficiently powered to detect significant differences in the secondary outcome variable.

Therefore, to conclude, the intrathecal dexmedetomidine (3 µg) is more efficacious as compared to intravenous dexmedetomidine (0.5 µg/kg) bolus as adjuvant to subarachnoid block by virtue of favourable outcomes in terms of prolonged duration of analgesia along with decreased rescue analgesic requirement and improved pain scores.

However, further studies are necessary to assess the optimal dose, timing of dexmedetomidine infusion/bolus as an adjuvant to subarachnoid block to ensure adequate postoperative analgesia and decreased pain scores without adverse effects.

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**Conflicts of interest**

There are no conflicts of interest.

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