Original Research Paper

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TO EVALUATE THE EFFICACY OF INTRAVENOUS DEXMEDETOMIDINE AS ANALGESIC ADJUVANT ON POST OPERATIVE DELIRIUM IN ORTHOPAEDIC SURGERY PATIENTS- A RANDOMIZED CONTROL TRIAL

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ABSTRACT **Background:** Dexmedetomidine improves normal sleep architecture; the drug also improves analgesia. We therefore tested the hypothesis that supplementing intravenous analgesia with dexmedetomidine reduces delirium in elderly undergoing orthopedic surgery. **Methods:** In this double-blinded randomized controlled trial, we enrolled 150 older (aged 65–90 years) patients scheduled for major orthopedic surgery. Postoperative analgesia was provided by intravenous fentanyl, supplemented by randomly assigned dexmedetomidine (1.25 µg/mL) or placebo, for up to three days. Primary outcome was the incidence of delirium assessed twice daily with the Confusion Assessment Method. Secondary outcomes, pain severity was assessed twice daily and sleep quality once daily, each with an 11-point scale where 0 = no pain/the best possible sleep and 10 = the worst pain/the worst possible sleep **Results:** The incidence of postoperative delirium was 13.1% (8 of 61) with placebo and 5.08% (3 of 59) with dexmedetomidine; Dexmedetomidine reduced pain both at rest ($P \leq 0.001$) and with movement ($P < 0.001$) throughout the first 5 postoperative days; it also improved sleep quality during the first 3 postoperative days. **Conclusions:** Intravenous analgesia with low-dose dexmedetomidine reduced delirium significantly, and provided better analgesia and sleep quality without any serious adverse events.

KEYWORDS : Elderly, Orthopedic Procedures, Delirium, Dexmedetomidine, Postoperative Period

INTRODUCTION

Delirium is a disturbance in attention, cognition and awareness of an individual . It has a fluctuant course more common among elderly patients recovering from major orthopaedic surgery. ICD-10 also includes psychomotor disturbances , disturbance of sleep –wake cycle and emotional disturbances in definition of delirium .Post operative delirium may be due to severe pain, sleep disturbances , opioids & inflammation caused due to the stress of anesthesia and surgery.

Dexmedetomidine is an □2 adrenergic agonist used as an adjuvant for procedural sedation ,analgesia & anxiolysis in anesthesia pharmacologic armantarium nowadays. Dexmedetomidine also improves sleep quality by increasing total S2 NREM sleep cycle.

The demand for orthopedic surgery is increasing nowadays, especially amongst the elderly population. Delirium is a common entity amongst these elderly patients recovering from major orthopedic surgery with reported incidence ranges from 5 to 14% after total joint arthroplasty[1], and from 12 to 56% after hip fracture surgery[2]. Patients who experience postoperative delirium(POCD) have worse outcomes including prolonged hospitalization, increased costs, lower chances of early home discharge, more re-admissions, delayed functional recovery, and increased perioperative and long-term mortality[3-4]. While delirium is now recognized as a serious cause, there is still so far no convincing evidence that any preventive strategy is effective[5] in reducing the amount of trauma caused by it.

POCD is probably related to several factors which may include severe pain [6], opioid medication[7], sleep disturbances[8], and the stress response and inflammation consequent to surgical tissue injury[8].

Dexmedetomidine is a highly selective alpha-2-adrenergic agonist with sedative, analgesic, and anxiolytic properties. For postoperative patients, low-dose intravenous infusion can promote normal sleep patters by increasing total and stage 2 non-rapid eye movement sleep but not rapid eye movement sleep[9]. When used in combination with opioids after surgery, it improves analgesia and sleep quality while reducing total opioid consumption [10-11]. The drug also attenuates the surgical stress response and consequent inflammation[12]. These characteristics makedexmedetomidine a drug of choice for delirium prevention. A study elucidates that when used during anesthesia or in the intensive care unit, it reduces postoperative delirium[13].

We therefore aimed to test the primary hypothesis that supplementing intravenous analgesia with dexmedetomidine reduces delirium in elderly patients recovering from major orthopedic surgery in the Bundelkhand region. Secondarily, we tested the notion that dexmedetomidine supplementation also improves analgesia and subjective sleep quality in elderly in the postoperative period.

The study was conducted on patients of either sex aged 65-90 years, ASA physical status I & II scheduled for Hip Arthroplasty /hip fracture repair under Combined Spinal Epidural anesthesia. A prior approval from the medical ethical committee of MLB medical college was taken.

MATERIALS AND METHODS

A written and informed consent was taken from all the patients included in the study . The designed study was conducted from January 2022-August 2022.

STUDY DESIGN: Randomized Control Double Blinded Trial

AIMS AND OBJECTIVES

Primary objective: To assess the role of intravenous dexmedetomidine in prevention of post operative delirium in elderly population undergoing major orthopaedic surgeries

Secondary objective: To evaluate postoperative analgesia and subjective sleep quality in elderly patients.

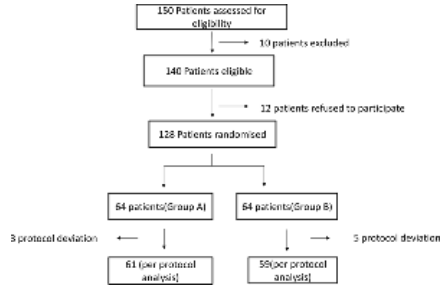
Inclusion Criteria	Exclusion Criteria
• Patients aged 65–90 years. • ASA I & II • Scheduled for elective hip or knee arthroplasties, hip fracture repair.	• Not giving consent • History of schizophrenia, epilepsy, parkinsonism, or myasthenia gravis. • BMI >30 • Diagnosed sleep apnea syndrome or a STOP-Bang score≥3

1) Group A : Normal saline (0.9%) 100 ml infused over the duration of surgery and continued for 24 hours postoperatively.

2) Group B : Dexmedetomidine infusion diluted in 100 ml saline ,started after Central neuraxial blockade at dose 0.4 mcg/kg/hour over

the duration of surgery and continued at 0.1 mcg/kg/hour till 24 hrs postoperatively.

STUDY DESIGN



Rescue Analgesia was provided with : IV Paracetamol 1gm Infusion BD and Epidural top ups with fentanyl 50 mcg if NRS > 5.

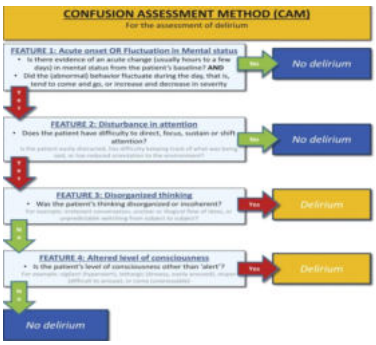
Patients were transferred to the post-anesthesia care unit(PACU) for 30 min, and were then sent to orthopaedic ward. Electrocardiogram, non-invasive blood pressure, and pulse oxygen saturation were monitored continuously in the ward until next morning. Non-invasive blood pressure and heart rate were monitored twice daily until hospital discharge. Those with unstable hemodynamics were transferred to an intensive care unit if necessary.Non-pharmacological strategies to reduce delirium, included restoration of hearing and vision aids, reorientation, behaviourial and cognitive therapy, early mobilization, sleep-promotion and correction of dehydration in all patients[14]. Patients with delirium were initially managed with non-pharmacological measures and were asked to continue medication of their primary diseases. Severe agitation (RASS score of□ +□ 3 or more) was treated with haloperidol[15] and flupenthixol.

EVALUATION SCORES USED IN OUR STUDY

Mini-Mental State Examination (MMSE; scores range from 0 to 30, with higher scores indicating better cognitive function) -cognitive performance .

Our main objective was to assess delirium, which was evaluated twice daily, using CAM (Confusion Assessment Method)

NRS - to evaluate intensity of postoperative pain , both at rest and while moving , subjective sleep quality once each day



SAMPLE SIZE ESTIMATION

Based on previous studies[16-17], we expected that delirium would occur in 12.5% of elderly patients after orthopedic surgery in the placebo group. In a recent trial, low- dose dexmedetomidine reduced postoperative delirium by about 60%[18]. Henceforth we assumed that delirium would be reduced by atleast 50% in the dexmedetomidine study group B. With significance set at 0.05 and power set at 80%, the sample size was 120 patients. Anticipating about 5% loss-to-follow-up, we planned to enroll 150 patients. Sample size was calculated with the PASS 11.0 software (Stata Corp. LP, College Station, TX, USA).

OBSERVATIONS

Table 1: Baseline data

	GROUP A (n□=□61)	GROUP B (n□=□59)	ASD
Age (year)	71□±□5	70±4	0.042
Male sex	19(31.1%)	20 (33.8%)	0.014
Body mass index (kg/m)	26.1□±□3.5	26.0□±4.□2	0.042
MMSE (score)	26.5+3.2	25.1+3.9	0.032

Baseline data included demographic characteristics included age, sex, bodymass index[19]. During the pre-operative interview, cognitive function was evaluated with the Mini-Mental State Examination score (MMSE; scores range from 0 to 30, with higher scores indicating better cognitive function)[20].

Table 1

Routine intra-operative monitoring included electrocardiogram, non-invasive blood pressure, pulse oxygen saturation and urine output. Central venous pressures were monitored when clinically indicated. Other intra-operative data included the duration of anesthesia, doses of medication during anesthesia, type and duration of surgery, estimated blood loss, administered fluid volumes, and blood transfusions. Adverse events were monitored from the beginning of post-operative analgesia until 72 h after surgery.Among anticipated abnormalities, we defined bradycardia as heart rate□<□45 beats per minute, hypotension as systolic blood pressure□<□90 mmHg or a decreased of more than 30% from baseline, tachycardia as heart rate□ >□ 100 beats per minute, hypertension as systolic blood pressure□>□180 mmHg or an increase of more than 30% from baseline, and hypoxemia as pulse oxygen saturation□<□90% all the hemodynamic parameters were not statistically significant in both

Table 2

Postoperative data included amount of rescue drug paracetamol used, and epidural fentanyl consumption during postoperative period, and other medications Interview for Cognitive Status-modified (TICS-m; scores range from 0 to 48, with higher scores indicating better function[21].

Table 2

Intraoperative and postoperative management			
	group A (n = 61)	Group B (n = 59)	P value
Postoperative data within 72 hours			
Use of paracetamol infusion(n-patient)	49(82.5%)	41 (59.4%)	0.407
Use of epidural fentanyl	31(18.3%)	19(14.6%)	0.365

Table 3

Postoperative pain severity was assessed twice daily, between 8–10 AM and between 6–8 PM, with the NRS, both at rest and with movement. “Movement” was defined as turning over on/getting off the bed for patients after joint surgery. The most severe pain score during movement was recorded.

Subjective sleep quality was assessed once daily, between 8–10 AM, with the NRS. Patients were asked to give a score that best evaluates their overall sleep quality, i.e., a good night’s sleep or a bad night’s sleep. The scale ranged from 0 to 10, with 0 representing the best possible sleep and 10 the worst possible sleep. A minimum difference of 1 point was considered clinically meaningful[22]length of hospital stay was assessed in both the groups which was statistically significant.

Table 3

	Group A (n□=□61)	Group B (n□=□59)	P value
Overall incidence of delirium (per-protocol analysis)	8 (13.1%) (n□=□61)	3 (5.08%) (n□=□59)	0.04
Pain severity(NRS scale) Rest Movement	5/10 9/10	4/10 6/10	
Length of hospital stay (day)	7 (7, 6)	5 (5, 6)	0.593
Sleep(NRS)	5	3	

STATISTICAL TESTS USED

- The balance of baseline data between groups was assessed using absolute standardized difference, calculated as the absolute difference in means, medians, or proportions divided by the pooled standard deviation[23].
- The primary outcome, i.e., the incidence of delirium within 3 days after surgery, was compared with chi square tests, with differences between groups expressed as relative risk (95% CI)
- Other numeric variables were analyzed using independent-sample t tests. Differences (and 95% CIs for the differences) between medians were calculated with Hodges-Lehmann estimators. Categorical variables were analyzed using chi square, or Fisher

exact tests

- For all hypotheses, two-tailed P values < 0.05 were considered statistically significant. P values < 0.10 were considered statistically significant. Statistical analyses were performed on SPSS 25.0 software package (IBM SPSS, Chicago, IL).

RESULTS

120 patients scheduled for orthopaedic surgery were randomly allocated to receive either i/v dexmedetomidine(n = 59) or a placebo (n = 61) during the designed study Demographic data was comparable between the two groups (Table 1). Intraoperative haemodynamics, epidural fentanyl usage, and use of additional analgesics, viz paracetamol throughout the first three postoperative days were similar in each group.

Postoperative delirium struck 8 of 61patients (13.1%) who received a placebo and 3 of 59 patients (3%) who received dexmedetomidine: relative risk 0.65, 95% confidence interval (0.36 to 1.18), p = 0.04.

Pain severity at rest and during movement (NRS) was lower in dexmedetomidine group across first 3 postoperative days with less opioid consumption in this group Subjective sleep Quality was better in dexmedetomidine group than placebo group during postoperative periodLength of hospital stay was found to be statistically lower in study group.

The frequency of negative outcomes (postoperative nausea, vomiting, dizziness, headache) was comparable between the two groups. There were no serious adverse effects during the trial period.

DISCUSSION

Hong *et al*. (2021) and Deiner *et al*., (2017) has established a study on Impact of dexmedetomidine supplemented analgesia on delirium in patients recovering from orthopedic surgery and meta-analysis of multiple RCTs.

Sun *et al*. has established a study on delirium incidence, pain scoring at rest & movement ,supplemental analgesics & subjective sleep quality.YEAR?

In these previous studies, administration of dexmedetomidine significantly reduced delirium in patients [24-25]. In the present study, we adopted a dosing regimen (mean infusion rate 0.4 $\mu g.kg^{-1}.h^{-1}$) even lower than in previous studies in order to avoid potential side effects including sedation[26] prudence is necessary when administering dexmedetomidine in postoperative patients, especially those in the general ward. In a recent trial of 798 participants having cardiac surgery, evenmoderate dose dexmedetomidine (0.1–0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ until 24 h postoperatively) increased clinical important hypotension[27].

Orthopedic surgery is associated with severe postoperative pain which impairs recovery by increasing complications including delirium[6]. Multimodal analgesia is thought to relieve pain after orthopedic surgery but these regimens do not include dexmedetomidine. In our study patients, dexmedetomidine reduced NRS pain scores at rest and with movement. Our results are consistent with Shin *et al*.[28] who reported improved analgesia for up to 48 h.

Interestingly, the analgesic benefits provided by dexmedetomidine extended beyond its biological half-life of 2 h. Specifically, analgesia was improved throughout 3 days of recovery Supplemental dexmedetomidine thus appears to be a good strategy for relieving postoperative pain although further studies are required to confirm our findings.

Low-dose dexmedetomidine improves subjective sleep quality [29]. by reducing stage N1 sleep, increasing stage N2 sleep, and increasing sleep efficiency[27]. As expected, we found that dexmedetomidine improved subjective sleep quality during the first 3 postoperative days. Dexmedetomidine might have improved sleep by activating endogenous sleep pathways[30]. Also,good analgesia improves postoperative sleep[31]. In our results, dexmedetomidine did not cause excessive sedation or hemodynamic fluctuations, suggesting that the drug in current dose is a safe sedative and analgesic adjuvant

CONCLUSION

Administration of perioperative dexmedetomidine reduced the incidence of postoperative delirium in adult patients above 65 years of age undergoing Orthopaedic surgeries.

Postoperative pain & Sleep Quality was also improved by administration of Dexmedetomidine with reduced hospital stay.

Limitation of study: the sample size can be further expanded with more inclusion of other complicated surgeries also we did not include patients with severe comorbities the potential long term complications of delirium could be followed up for after a week too.

Conflict of interest-none

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