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RESEARCH ARTICLE

Perioperative oral pregabalin or clonidine in patients undergoing lumbar spine posterior fusion: A randomized controlled trial

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ABSTRACT

Background: Multiple techniques and pharmacological efforts have been tried to control intraoperative hemodynamic fluctuations, reduce perioperative blood loss and severe postoperative pain. This study aimed to assess the perioperative effects of oral premedication with pregabalin or clonidine for lumbar spine posterior fusion under general anesthesia (GA). Outcome measures: Perioperative blood loss, hemodynamics, anesthetics consumption, postoperative pain, and side effects

Methods: This is a prospective, triple blinded randomized placebo-controlled trial (RCT). Ninety-six adult ASA I-II patients of either sex undergoing lumbar spine posterior fusion were randomly assigned to obtain a placebo (group E), pregabalin 300 mg (group P), or clonidine 200 µg (group C) orally 90 minutes before induction of GA. Trial registration: www.pactr.org with (PACTR201710002416280).

Results: Preemptive oral pregabalin 300 mg and clonidine 200 µg optimized intraoperative hemodynamics, reduced perioperative blood loss than the placebo group (by 22.2% and 30.7%, respectively), reduced postoperative pain scores, and anesthetic and postoperative analgesic consumption. In addition, they prolonged the duration to the first postoperative analgesic request. There was no major complication in any group.

Conclusion: Premedication with pregabalin or clonidine reduced perioperative blood loss and optimized intraoperative and postoperative hemodynamics, with the preference for clonidine over pregabalin as well as both reduced postoperative pain scores, analgesic requirements, PONV, and shivering. Sedative drugs should be used in lower doses to avoid oversedation. Pregabalin-associated dizziness and visual disturbance may necessitate extra precautions and patient education.

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Pregabalin; clonidine; blood loss; lumbar spine fusion

1. Introduction

Spine surgeries are associated with considerable intraoperative hemodynamic fluctuations, blood loss, and severe postoperative pain [1,2]. Avoidance of hemodynamic fluctuations decreases blood loss, reduces blood transfusion requirements, and allows better visualization of the surgical field thus increasing the quality of the surgery [3].

Adequate control of postoperative pain allows early mobilization, improves patient satisfaction, shortens hospital stays, and prevents the development of chronic pain [4,5].

High doses of opioids and/or anesthetic agents can optimize the hemodynamics and hence decrease blood loss; However, this may interfere with neurophysiological monitoring, delay emergence from anesthesia, precipitate postoperative nausea and vomiting (PONV), over sedation, pruritus, and the development of acute tolerance [6].

A combination of opioids and non-opioid analgesics such as (antihyperalgesic e.g., pregabalin or α_2 agonist e.g., clonidine) as a part of multimodal analgesia reduces opioid requirements and potentiates the opioid analgesic impacts without increasing their hyperalgesia properties and side effects [7–9].

Pregabalin exists as a lipophilic gamma amino butyric acid (GABA) analog with analgesic, anxiolytic, antihyperalgesic, and anticonvulsant characteristics [10]. Clonidine is an α_2 agonist, it hyperpolarizes the presynaptic neurons involved in pain transmission and reduces the sympathetic outflow [1,11].

Our prospective study aimed to assess the perioperative effects of a single oral dose of pregabalin or clonidine in patients undergoing lumbar spine posterior fusion.

2. Patients and methods

The present triple-blinded randomized placebo-controlled trial (RCT) runs in concordance with the

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Consolidated Standards of Reporting Trials (CONSORT) policies. The study was approved by the local ethics and research committee of the Anesthesia, Department of Menoufia University, and was registered at www.pactr.org with (PACTR201710002416280).

The study was performed in the hospitals of Menoufia University between August 2018 and June 2020. Ninety-six (96) patients scheduled for lumbar spine posterior fusion aged 18–65 years old of either sex, with American Society of Anesthesiologists physical class (ASA) I or II were incorporated in the study. The participants were randomized to three groups (32 patients each) based on the premedication drug by a computer-generated random allocation to guarantee appropriate opacity of our study management from the anesthetist who gave study drug preoperatively, patients and assessors till the definitive results extraction. An informed written acceptance was acquired from all patients before surgery. The premedication drug was provided orally with little gulps of water 90 minutes before induction of general anesthesia (GA). Group P received a 300 mg pregabalin capsule (Gabapentin Capsule®, Enhua Pharmaceutical Limited by Share Ltd., Jiang Su, China), Group C received a 200 µg clonidine tablet (Catapres tablet®, Boehringer Ingelheim, Germany), and Group E received a placebo (empty) capsule.

Exclusion standards were the patient refused to participate, allergy to any of the study drugs, previous spine surgery or back pain intervention, history of a bleeding disorder or recent anticoagulant or β-blockers therapy; body mass index ≥35 kg/m^2; and those unable to understand the visual analogue scale (VAS).

The preoperative estimation and anesthesia techniques were standardized in all groups. On arrival at the operating theatre, IV infusion of 7 ml/kg/hr. of warmed lactated ringer was started. Continuous electrocardiography, pulse oximetry, continuous arterial blood pressure, capnography, bispectral index (BIS), and peripheral nerve stimulator (PNS) were applied.

After preoxygenation, we induced GA by IV 2 mg/kg propofol, 2 µg/kg fentanyl, and 1 mg/kg lidocaine. Cisatracurium (0.15 mg/kg) was utilized to simplify oral tracheal intubation followed by top-up doses (0.03 mg/kg) guided by PNS. Anesthesia was maintained with isoflurane (1–1.2%), to maintain the BIS at 40–50. Mechanical ventilation with 7 ml/kg tidal volume and respiratory rate was adjusted to keep an $ETCO_2$ of 30–35 mmHg in an air/oxygen mixture (1:1). 1 mg granisetron was slowly infused for prophylaxis against PONV. All patients underwent the same surgical technique by the same surgical team.

The study protocol defined hemodynamics (mean ABP and HR) targets were within 20% of the baseline values. Intraoperatively, if mean ABP or HR increased above the target value with accepted BIS, ETCO2, SPO2, and PNS readings, IV fentanyl (0.5 µg/kg) bolus was given. If they remained above target, 0.5 µg/kg/min nitroglycerine was started for 5 minutes and titrated gradually until the achievement of target hemodynamics. Toward the end of the surgery, IV Acetaminophen (1 gm) was slowly infused.

Postoperatively, IV 1 gm Acetaminophen was given every eight hours on the 1st postoperative day. If VAS became ≥ 4, IV ketorolac (30 mg) over 10 min, then repeated every 12 hours. If VAS was still > 4, IV meperidine (0.5 mg/kg) every 30 minutes till VAS became < 4.

The primary outcome was perioperative blood loss. Blood loss was recorded as intraoperative (volume in the suction container in addition to the count and quality of the soaked gauze pads; minimal = 5 ml, moderate = 10 ml, and heavy soaking = 15 ml blood), as well as postoperative total 24 hours' suction container volume. Secondary outcomes included hemodynamic parameters, postoperative pain and analgesic requirements, perioperative sedation level, and the incidence of side effects (PONV, shivering, headache, visual disturbance, dizziness, and mouth dryness). Hemodynamics were recorded before the premedication, 60 minutes after the premedication, 1,3,5 minutes after intubation, every 5 minutes intraoperatively, and every 15 minutes for 1.5 hours postoperatively. The postoperative pain was evaluated hourly for 24 hours by VAS as well as the time of 1st analgesic request. Ramsay Sedation Scale [12] was recorded before premedication before induction of anesthesia and 15 minutes after extubation. Surgeon satisfaction with a bloodless field was assessed as good (minimum bleeding), moderate (that impairs the operating condition), and virulent (substantial bleeding that impairs the operating conditions).

2.1. Statistical analysis

Power analysis: A statistical power analysis was achieved after sample size accounting, based on data from the current study ($N = 96$), comparing Group P to Group C. The effect size (ES) for blood loss in this study was 1.49, considered to be large using Cohen's (1988) standards, with an alpha = 0.05 and sample size = 32 in every group, a post-hoc power analysis was achieved with this effect size (GPower 3.1) and it is around (1-ß) = 0.99. Thus, our power analysis for a sample size of 32 in each group is satisfactory for the main objective of this study. An equal number for Group E (control group) was assigned.

SPSS 21 software (SPSS Inc. USA) was utilized to analyze the data. Quantitative data were described as mean ± standard deviation(M ± SD), and ANOVA (analysis of variance) was utilized for comparison. This was tracked by post hoc tests (LSD) if there was a statistical difference between the groups. Scores were defined as median (Min.-Max.)

and analyzed by Kruskal – Wallis H test. If a statistical difference was detected, the comparison between groups was achieved by using post hoc tests (Mann-Whitney U test). The chi-square $\chi 2$ test was used to compare 2 or more qualitative groups in the categorical data. p values less than 0.05 were assumed statistically significant.

3. Results

One hundred seventeen (117) patients were evaluated for eligibility; 21 patients were excluded, and 96 patients completed the study, they were randomly assigned to 3 groups (Figure 1). There were no statistically significant differences in demographic data, surgery duration, or baseline hemodynamics between the study groups (Table 1).

Pregabalin and clonidine groups retained significantly less total blood loss than the control group (730.3 ± 121.2 & 650.0 ± 93.3 versus 938.4 ± 141.5 ml, respectively) ($p < 0.001$). Furthermore, Intraoperative blood loss was significantly less in the clonidine group than pregabalin group (437.8 ± 67.9 versus 505.0 ± 118.7 l) ($p = 0.007$), while the postoperative blood loss was comparable between pregabalin and clonidine groups (($p = 0.363$) (Table 2).

After 90 minutes of oral premedication of the study drugs, the hemodynamic parameters were significantly higher in the control than pregabalin and clonidine groups at all-time points. The HR was similar between pregabalin and clonidine groups at all-time points (Figure 2), but the MAP was significantly less in the clonidine group than pregabalin group before the intubation ($p < 0.001$), then, it was comparable between the two groups at the residual time points (Figure 3).

There were no significant differences between the pregabalin and clonidine groups in total intraoperative isoflurane, fentanyl, and nitroglycerine consumption (Table 2). While they were higher significantly in the control group ($p < 0.001$). Furthermore, the top-up doses of IV fentanyl bolus (0.5 µg/kg) to maintain the

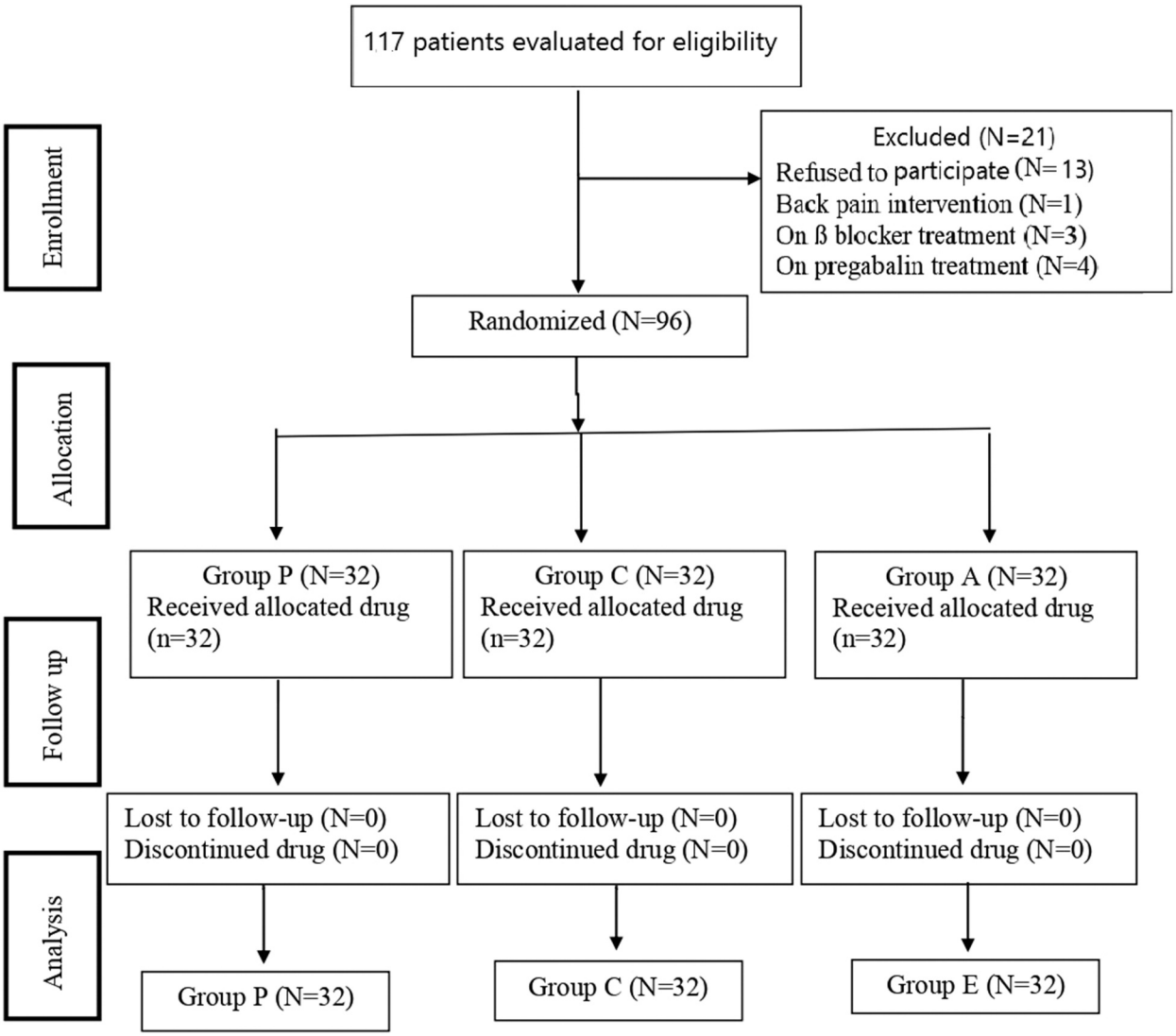

Figure 1. Consolidated standards of reporting trials (CONSORT) flow diagram.

Table 1. Comparison of the demographic data and surgery time of the studied groups.

Demographic data	Group E ($n = 32$)	Group P ($n = 32$)	Group C ($n = 32$)	p-value
Age (y)	52.4 ± 6.7	49.9 ± 7.3	53.1 ± 6.2	0.144 *
Sex M/F	15/17	13/19	12/20	0.741 ¥
Weight (kg)	81.6 ± 9.8	82.3 ± 9.9	85.6 ± 7.5	0.181*
Height (cm)	167.8 ± 6.3	165.4 ± 6.5	169.1 ± 6.9	0.081*
BMI (Kg/M^2)	29.1 ± 3.8	30.1 ± 3.4	30.0 ± 2.9	0.398*
ASA (I/II)	16/16	14/18	17/15	0.747 ¥
Surgery time (min)	159.4 ± 28.8	162.8 ± 26.3	156.6 ± 30.1	0.680 *

Data were expressed in mean ± SD. * : One way ANOVA ¥: Chi-square test.
P: p-value for comparing between the three studied groups.

Table 2. Comparison between the three studied groups according to different parameters.

	Group E ($n = 32$)	Group P ($n = 32$)	Group C ($n = 32$)	p-value
Total perioperative Blood loss	$938.4^a \pm 141.5$	$730.3^b \pm 121.2$	$650.0^c \pm 93.3$	<0.001*
Intraoperative Bl loss (ml)	$668.6^a \pm 98.9$	$505.0^b \pm 118.7$	$437.8^c \pm 67.9$	<0.001*
24-hour ready vac content (ml)	$269.8^a \pm 72.8$	$225.3^b \pm 48.2$	$212.2^b \pm 47.6$	<0.001*
Fentanyl consumption (mic)	$227.1^a \pm 4.9$	$173.3^b \pm 3.9$	$175.7^b \pm 2.8$	<0.001*
No. of patients needed top-up fentanyl	$32/32^a$ (100%)	$4/32^b$ (12.5%)	$3/32^b$ (9.4%)	<0.001 ¥
Nitroglycerine consumption (mic)	$356.3^a \pm 5.9$	$41.6^b \pm 1.7$	$24.0^b \pm 1.4$	<0.001*
No. of patients needed nitroglycerine	$11/32^a$ (34.4%)	$2/32^b$ (6.2%)	$1/32^b$ (3.1%)	<0.001 ¥
Isoflurane consumption (ml)	$79.2^a \pm 14.3$	$66.8^b \pm 10.5$	$62.3^b \pm 11.5$	<0.001*
Surgeon satisfaction Good	21 (65.6%)	25 (78.1%)	29 (90.6%)	0.200 ¥
Moderate	7 (21.9%)	5 (15.6%)	2 (6.2%)	
Virulent	4 (12.5%)	2 (6.2%)	1 (3.1%)	
Time to 1^{st} postop analgesic request (min)	$70.9^a \pm 10.1$	$170.6^b \pm 11.5$	$158.3^c \pm 10.4$	<0.001*
24 hours Ketorolac consumption (mg)	$90.0^a \pm 0.0$	$62.8^b \pm 1.4$	$70.3^c \pm 1.5$	<0.001*
24 hours meperidine consumption (mg)	$114.7^a \pm 2.1$	$80.9^b \pm 4.5$	$87.0^b \pm 3.7$	0.001*
Sedation score before GA induction	1^a (1–3)	1^a (2–3)	2^b (2–3)	0.005 H
Sedation score (15 minutes after extubation)	1^a (1–2)	3^b (1–4)	2^b (1–4)	<0.001 H
Dizziness	1^a (3.1%)	10^b (31.3%)	3^a (9.4%)	0.004 ¥
Visual disturbance	0^a (0.0%)	5^b (15.6%)	1^a (3.1%)	0.024 ¥
PONV	6^a (18.8%)	1^b (3.1%)	1^b (3.1%)	0.033 ¥
Shivering	7^a (21.9%)	2^b (6.2%)	1^b (3.1%)	0.031 ¥
Dry mouth	1 (3.1%)	1 (3.1%)	5 (15.6%)	0.085 ¥
Headache	5 (15.6%)	2 (6.3%)	2 (6.3%)	0.332 ¥

* : One way ANOVA test, Pairwise comparison between each 2 groups was done using **Post Hoc Test (LSD)**.
¥: **Chi-square test**. H: H for **Kruskal Wallis test**.
Different letters (a, b, c) are significant (i.e. **Common letters** are not significant).
p: *p* value for comparing between the studied groups.

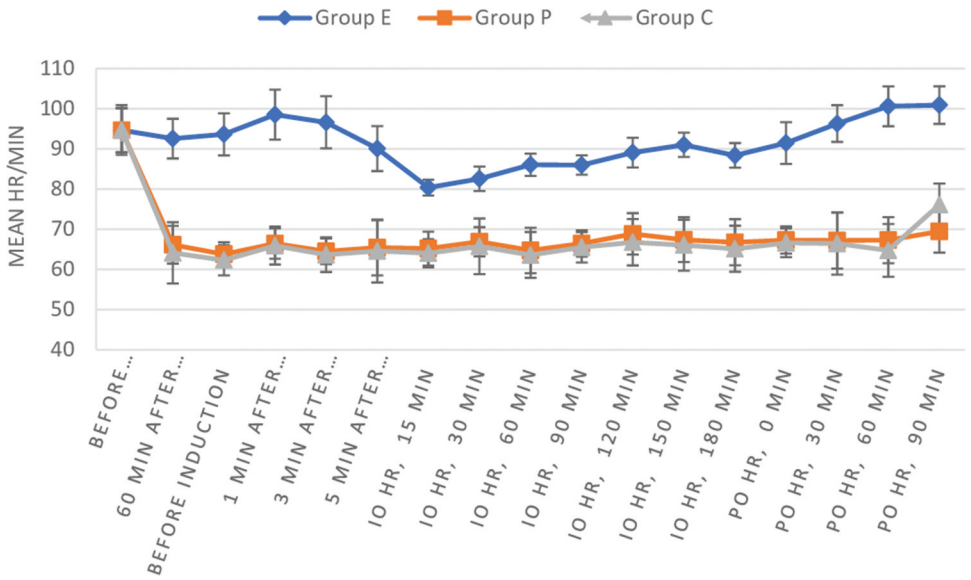

Figure 2. Comparison of the intraoperative and postoperative heart rate (Beats/min.) between the study groups.

targeted hemodynamics were needed in 4 patients (12.5%) in pregabalin and 3 patients (9.4%) in clonidine groups; in comparison to all patients of the control group. Moreover, nitroglycerine infusion (0.5 µg/kg/min) was needed in only 2 patients (6.3%) in pregabalin and 1 patient (3.1%) in clonidine groups; in comparison to 11 patients (34.4%) of the control group then it was upregulated to (1 µg/kg/min) in 4 patients (12.5%) of them (Table 2).

Surgeon satisfaction was good for a bloodless field in 29 patients (90.6%) of the clonidine group compared to 25 patients (78.1%) of the pregabalin group and 21 (65.6%) of the control group, this difference was significant statistically between clonidine and control group only ($p = 0.016$) (Table 2).

Pregabalin and clonidine groups had a significantly prolonged duration to the first postoperative analgesic request than the control group ($p < 0.001$); moreover, this duration was significantly longer in pregabalin than clonidine group ($p < 0.001$). Furthermore, the control group had significantly more postoperative ketorolac (30.2% & 21.9%) and meperidine (29.5% & 24.1%) requirements than pregabalin and clonidine groups respectively. Ketorolac requirement was significantly lower in pregabalin than clonidine group ($p = 0.011$) while meperidine requirement was comparable between them ($p = 0.501$) (Table 2).

Pregabalin and clonidine significantly alleviated postoperative pain at all time points than the placebo group. However, VAS was significantly lower in pregabalin than clonidine group up to 12 hours postoperatively, then it was of comparable values at the remaining time points (Figure 4)

Before induction of anesthesia, the sedation score was significantly higher in the clonidine group than the others ($p < 0.001$). As well, it was significantly higher in clonidine and pregabalin groups 15 minutes after extubation ($p < 0.001$). However, no heavy sedation score (score >4) was detected in any group.

Postoperative dizziness and visual disturbance were quite more in the pregabalin group (31.3% and 15.6, respectively). Also, the postoperative PONV and shivering (18.8% and 21.9%, respectively) were significantly higher in the control group. Five patients (15.6%) in the clonidine group complained of dry mouth, and five patients (15.6%) in the control group complained of mild headache.

4. Discussion

Multiple methods and pharmacological measures have been tested to reduce perioperative blood loss and control intraoperative hemodynamic fluctuations. The present study demonstrated a more favorable hemodynamic profile and a significant reduction in intraoperative and postoperative blood loss after oral pregabalin (300 mg) or clonidine (200 µg) premedication for lumbar spine posterior fusion.

Pregabalin is a GABA analog that binds to the α_2 delta subunit of the presynaptic voltage-gated calcium channels that have a wide distribution over the nervous system [8–10]. It prevents the neuropathic component of acute surgical pain and reduces analgesic requirements [13,14]. Clonidine activates α_2 receptors in the brain and spinal cord resulting in sedative, analgesic, and anesthetic sparing effects. It decreases the sympathetic and stimulates the parasympathetic outflows and so attenuates the perioperative stress responses [1,11].

In the present study, despite maintenance of the protocol-defined hemodynamic targets, the placebo group had significantly higher intra- and postoperative

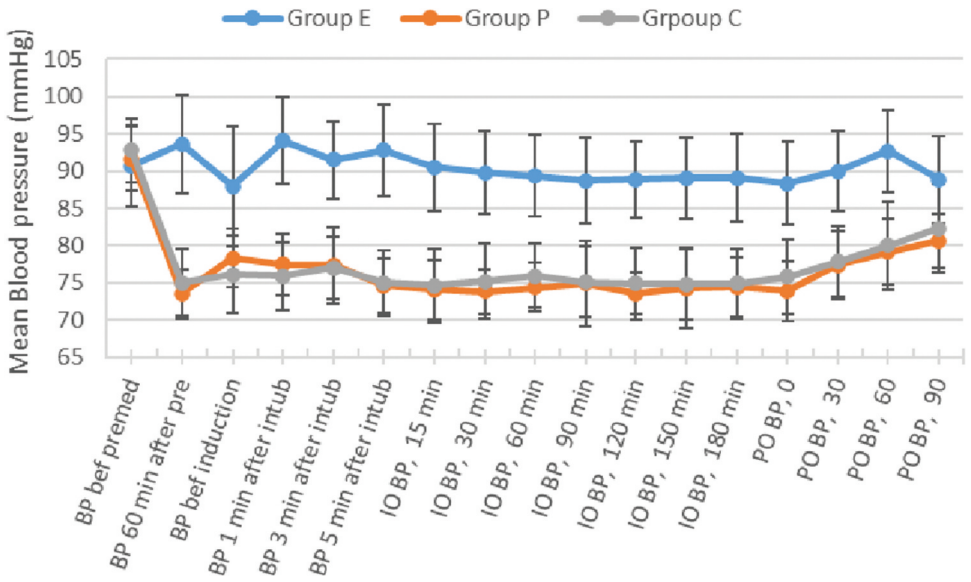

Figure 3. Comparison of the intraoperative and postoperative mean arterial pressure(mmHg) between the study groups.

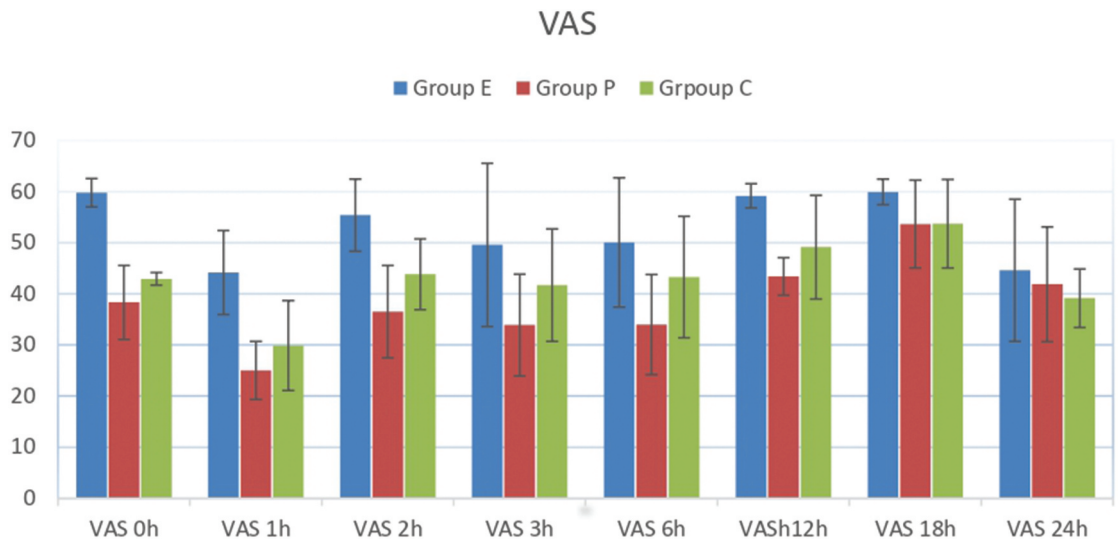

Figure 4. Comparison of VAS between the study groups.

blood loss than pregabalin or clonidine groups. Similar findings were reported by other researchers [1,11], a possible explanation is that the intraoperative hemodynamic variables in the placebo group are closer to the upper limit of the protocol-defined values.

Intraoperative blood loss was significantly less in the clonidine group than in the pregabalin group despite comparable HR and insignificantly lower BP in the pregabalin group. This may be attributed mainly to the pregabalin-associated antiplatelet effect [15,16]. Nevertheless, the postoperative blood loss and the hemodynamic variables were comparable between the two groups as a single preoperative dose of pregabalin may not have a prolonged antiplatelet effect for the postoperative period.

Lee et al., [17] noted a variation in the blood flow in the paraspinal muscle at similar grades of hypotension with different drugs. Moreover, clonidine may have a similar effect at higher blood pressure, consequently, the need for hypotensive anesthesia may be obviated. Furthermore, in spine surgery, bleeding is mainly venous due to bone decortication so it may not be affected by reduction of arterial blood pressure [18]. This may explain the significant difference in blood loss while keeping the hemodynamic parameters within the targeted range in all these study groups.

In concordance with other studies [11,19,20], the present study showed that pregabalin and clonidine premedication significantly attenuated the pressor response of laryngoscopy, intubation, and surgical incision. Besides, they stabilized the intraoperative hemodynamics in comparison to placebo despite the lower isoflurane and fentanyl consumption. Also, nitroglycerine infusion (0.5 µg/kg/min) was needed in 34.37% of these patients, that increased to (1 µg/kg/min) in 12.5%. to maintain the targeted hemodynamics. This is mostly related to the analgesic and/or the sympatholytic/parasympathomimetic effects of the study drugs.

Although the HR was significantly lower in the clonidine group before intubation and after that, it was insignificantly lower in the pregabalin group till the end of the study. Interestingly, there was no need for atropine for bradycardia in any group. This coincides with Gunasekaran et al. [21], despite the usage of double doses of pregabalin and clonidine than in our study. However, during laparoscopic cholecystectomy, Gupta K et al. [11] used a similar clonidine dose to ours, but they reported bradycardia in 15% of their cases. This may be attributed to the vagal effect during the creation of pneumoperitoneum.

Concerning the surgeon's satisfaction with a bloodless surgical field, it was good in all the study groups. However, while being comparable between clonidine and pregabalin, it was significantly better in clonidine than the placebo group.

Pregabalin premedication was associated with a significantly prolonged postoperative analgesia than clonidine premedication which in turn was significantly longer than placebo. This runs in concordance with other reports [22,23]. Moreover, the postoperative analgesia in the present research is significantly longer than that noted in other reports [4,24] This may be attributed to the higher pregabalin doses (300 mg) used in our study.

Our results support that of other investigators [4,7,25,26], that pregabalin premedication lowered the postoperative VAS scores than clonidine while being significantly lower in both than placebo premedication up to 12 hours postoperatively. On the contrary, Kim JC et al., and Urban MK et al., [14,27] reported insignificant differences in postoperative VAS between placebo and oral pregabalin (75 and 150 mg) given 1 hour preoperatively and 12 hours postoperatively in spine fusion surgeries. It was suggested that higher doses of pregabalin (≥300 mg/d) are associated with a significant reduction in VAS scores [7,14,28].

In consistency with other studies [7,10,24,29], the 24-hour postoperative analgesic requirements were significantly lower after pregabalin and clonidine premedication. There were 30.2% and 21.9% reductions in ketorolac consumption and 29.5% and 24.1% reductions in meperidine consumption in the pregabalin and clonidine groups respectively.

Clonidine-premedicated patients were significantly more sedated than pregabalin-premedicated ones. Both groups were associated with significantly higher sedation levels than placebo. Interestingly, no heavy sedation (score >4) was identified in any of the study groups. Similar findings have been reported by other investigators [7,11,30]

In consistency with other works [30–32], pregabalin-premedicated patients showed a higher incidence of dizziness and visual disturbance. Interestingly, Liu et al., [25] reported no significant differences between high and low-dose gabapentinoids in spine surgery in the occurrence of sedation, dizziness, headache, visual disturbance, somnolence, or urine retention. Contradictory to that, Tiippana et al. [33] and Jokela et al. [34] reported that higher doses (≥600 mg/day) were associated with potent analgesic effects, but at the expense of more frequent side effects while those <300 mg subsequently encouraged the analgesic effects.

None of the current study patients demonstrated any major complications. However, Eipe et al. [32] reported three cases that developed respiratory depression within the first 12 postoperative hours after high dose of pregabalin (450–600 mg); however, each of these patients had hazards that may contribute to respiratory depression (elderly patients, renal dysfunction, obstructive sleep apnea, or receiving neuraxial opioids).

Our study showed a potential benefit of both pregabalin and clonidine premedication as they reduced the incidence of PONV and shivering. This comes in agreement with previous studies [7,8,14,25,31] and that may be attributed to pregabalin and clonidine opioid-sparing effects or due to reduction in tachykinin and calcium influx in the area postrema by pregabalin inhibitory effects [35,36].

We believe that this study has some restrictions. Firstly: we have not considered the number of spinal segments being fused which of course affects the extent of tissue damage and consequently blood loss and postoperative pain. Second: we used fixed doses of study drugs regardless of the patient body weight. Third: we evaluated VAS at rest only. However, VAS at movement and mechanical pain threshold were not evaluated.

We conclude that in patients undergoing lumbar spine posterior fusion; oral pregabalin or clonidine premedication reduced perioperative blood loss and optimized the intra- and postoperative hemodynamic profile as well as reduced postoperative pain scores, analgesic requirements, PONV, and shivering. However, we recommend if pregabalin or clonidine premedication is used, other sedative agents should be used in lower doses to avoid oversedation. Pregabalin-associated dizziness and visual disturbance may necessitate extra precautions and patient education.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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