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RESEARCH ARTICLE

Effect of clonidine as an add-on to fentanyl premedication on post-operative pain in patients undergoing spine surgeries: A randomized study

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ABSTRACT

Background: Effective post-operative pain (POP) management begins in the pre-operative period as analgesics administered before surgical incision prevent central sensitization to pain. Fentanyl is a potent synthetic opioid, a most commonly used pre-anesthetic medication. Clonidine is an alpha-2 adrenoceptor agonist, used as a pre-anesthetic medication due to its nonopiate antinociceptive property that provides analgesia in the post-operative period. **Aims and Objectives:** The aims of the study were to study the effect of intravenous clonidine as an add-on to intravenous fentanyl premedication on POP in patients undergoing spine surgeries. **Materials and Methods:** Forty patients of the American Society of Anesthesiologists status I and II, aged 18–60 years of either sex, undergoing elective spine surgeries were randomized into two groups to receive premedications 30 min before anesthetic induction. Group C received intravenous infusion of clonidine 1.5 mcg/kg over 10 min along with slow intravenous injection of fentanyl 1 mcg/kg. Group F received slow intravenous injection of fentanyl 1 mcg/kg alone. After completion of surgery, patients were shifted to the post-operative recovery ward and on attaining modified Ramsay sedation score of 1, pain was assessed and recorded using numerical rating scale (NRS). **Results:** All the study participants completed the study and data were analyzed using per-protocol analysis. Baseline characteristics were comparable between the groups in terms of age, gender, body weight, and total duration of surgery. Sedation levels were found to be comparable between the groups. In Group C, all 20 patients had NRS score of either 4 or <4 and did not require rescue analgesia. In Group F, 8 patients had NRS score of more than 4 and required rescue analgesia. Absolute risk reduction was 40% ($P = 0.0014$) and number needed to treat was 3. No adverse drug reactions were reported for the entire study period. **Conclusion:** Intravenous clonidine 1.5 mcg/kg as an add onto premedication with intravenous fentanyl 1 mcg/kg decreased POP thus reducing requirement of rescue analgesia in patients undergoing spine surgeries.

KEY WORDS: Clonidine; Premedication; Fentanyl; Post-operative Pain; Numerical Rating Scale

INTRODUCTION

Pain management is an important prerequisite of anesthesia which can be achieved by the use of analgesics administered as pre-anesthetic medications. Among the analgesics, opioids are the most commonly used group of drugs in the perioperative period.[1]

Fentanyl is a synthetic opioid, a pethidine congener, most commonly used anesthetic premedication. It is 80–100 times more potent than morphine as an analgesic and rapidly enters the brain leading to peak analgesic effect within 5 min of intravenous injection.[2]

Clonidine is an alpha-2 adrenoceptor agonist used as pre-anesthetic medication due to its anxiolytic, sedative,

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and anesthetic sparing property. It stabilizes intraoperative hemodynamic parameters thus preventing morbidities and mortality due to adverse cardiovascular events. In addition, it has nonopiate antinociceptive property and can confer analgesia.[3] Hence, this study was undertaken to assess the effect of the addition of clonidine to fentanyl premedication, on post-operative pain (POP) in patients undergoing spine surgeries.

MATERIALS AND METHODS

Patient Selection and Assessment

After obtaining approval from the Institutional Ethics Committee with registration number BMCRI/PS/22/2019-20 dated 04 May 2019, this randomized open-label study was conducted between May 2019 and June 2019 in hospitals attached to Bangalore Medical College and Research Institute, Bengaluru. Forty patients of the American Society of Anesthesiologists status I and II, aged between 18 and 60 years, of either sex who underwent elective spine surgeries, were included in the study. Patients undergoing emergency spine surgeries and patients with psychiatric disorders, cardiovascular diseases such as hypertension, angina, and heart failure were excluded from the study. After obtaining written informed consent, eligible patients were randomized, in the ratio of 1:1, into two groups of 20 each using computer-generated simple randomization technique as depicted in Figure 1.

Group C (n = 20) received premedication with intravenous infusion of clonidine 1.5 mcg/kg over 10 min and slow intravenous fentanyl 1 mcg/kg under monitoring. Group F (n = 20) received slow intravenous fentanyl 1 mcg/kg alone. In addition, both the groups received premedications with slow intravenous injection of glycopyrrolate 4 mcg/kg, ondansetron 0.15 mg/kg, and pantoprazole 40 mg, 30 min before anesthetic induction.

All patients underwent anesthetic induction with intravenous propofol 2 mg/kg. Intravenous vecuronium 0.1 mg/kg was used as muscle relaxant. Sevoflurane was used as maintenance anesthetic such that the depth of anesthesia as per patient state index was between 25 and 50. After completion of surgery, sevoflurane was stopped and 100% oxygen was administered through the endotracheal tube. On voluntary respiratory efforts by the patient, reversal from muscle blockade was achieved using intravenous neostigmine 0.07 mg/kg with intravenous glycopyrrolate 0.2 mg/1 g of neostigmine. After the patients could vocalize and could obey verbal commands, they were shifted to post-operative recovery ward.

In the post-operative ward, when the level of sedation attained was 1 as per modified Ramsay sedation scale (MRSS), with the help of an anesthetist blinded about the study, pain was assessed using numerical rating scale (NRS) which is a unidimensional measure of pain intensity with a horizontal line segmented into 11 parts with integers from zero to ten where zero represents "no pain" and ten represents "worst imaginable pain." It also contains descriptive terms below the range of pain intensities, namely 0-no pain, 5-moderate pain, and 10-worst imaginable pain. This assessment tool was shown to the patient and asked to indicate the numerical value on the segmented scale which best described their pain intensity. The question was asked slowly, repeated if necessary and ample time was provided for the patient to comprehend the question and respond. The integer on the segmented scale which the patient pointed out was confirmed from the patient and recorded as the intensity of pain the patient was experiencing. If any patient-reported intolerable pain or if NRS score was found to be >4, intravenous pentazocine 30 mg was used as rescue analgesic.

Sample Size Estimation

The sample size was estimated considering 5% alpha error and 80% power. With an effect size of 5 and standard deviation of 5.44,[4] a sample size of 20 per group was estimated.

Statistical Analysis

Data were entered and analyzed using Microsoft Excel. Categorical data were represented as numbers and percentages and analyzed using nonparametric tests such as Chi-square

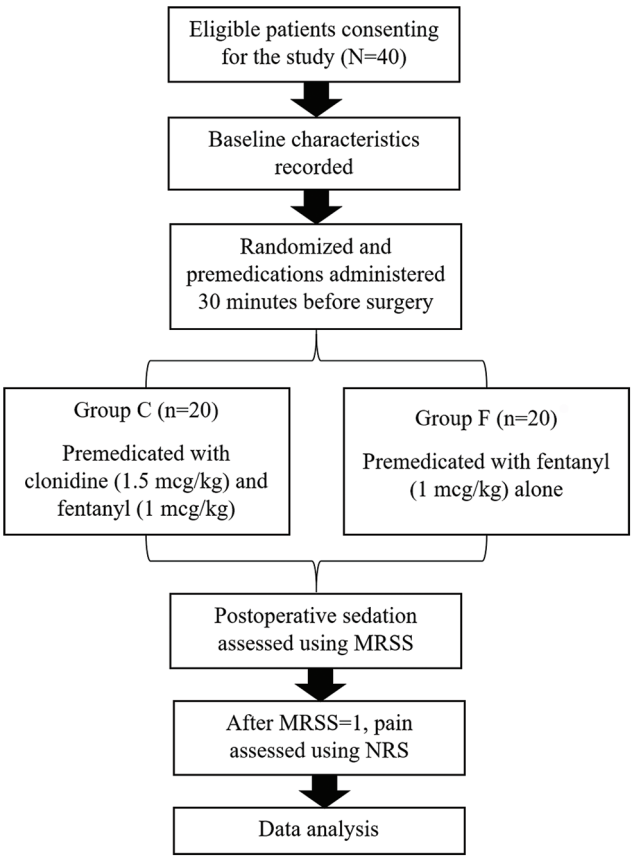

Figure 1: CONSORT participant flow diagram

test and Mann–Whitney U-test. Risk of intolerable pain (NRS score of >4) requiring rescue analgesia was calculated as absolute risk reduction (ARR) and number needed to treat with 95% confidence intervals (95% CI). Continuous data were represented as mean ± standard deviation and analyzed using parametric tests like unpaired "*t*"-test. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics were matched between the groups in terms of age, gender, body weight, and duration of surgery, as presented in Table 1.

Diagnoses are represented in Figure 2. Among 40 patients, 22 (55%) patients were diagnosed of intervertebral disk prolapse (IVDP) with 11 having cervical IVDP, 6 having lumbar IVDP, and 5 having lumbosacral IVDP. A total of 10 (25%) patients had mass lesions such as tumors and aneurysms causing compression to the spinal cord. The other diagnoses included spondylolisthesis and traumatic etiologies (2 [5%] each); and other miscellaneous causes of compressive myelopathy (accounting for a total of 3 [7.5%] cases).

There was no significant difference in the duration of surgery between the groups. Table 2 shows the MRSS and NRS scores of patients in each group. Among 20 patients in the clonidine group, assessment of sedation using MRSS immediately after shifting to recovery room showed that 2 (10%) patients were awake, 14 (70%) were lightly sedated, and 4 (20%) were moderately sedated but could follow simple commands. In the fentanyl group, 13 (65%) patients were awake and 7 (35%) were lightly sedated. There was no significant difference in the level of sedation between the two groups.

There was significant increase in the pain scores reported in the fentanyl group as compared to clonidine group. In the clonidine group, all 20 patients had NRS score of 4 or <4 and none of them required rescue analgesia. In the fentanyl group, 8 (40%) patients had NRS score >4 and required intravenous pentazocine 30 mg as rescue analgesia as represented in Figure 3. The difference in the proportion of patients experiencing intolerable pain was statistically significant ($P = 0.0014$) and ARR was 40% (95% CI: 18.53–61.47%) as shown in Table 3. Therefore, on average, 3 (95% CI: 1.6–5.4) patients would have to receive premedication with intravenous clonidine as an add onto intravenous fentanyl (instead of intravenous fentanyl alone) for one additional patient to not complain of intolerable pain in the post-operative period.

DISCUSSION

In the present study, the most common age group undergoing spine surgeries was 31–40 years with the mean age of

Table 1: Baseline characteristics between the groups

Parameter	Group C	Group F	*P* value
Age in years (Mean±SD)	41.1±12.66	43.55±15.07	0.581[$]
Gender			
Males	11	13	0.519[@]
Females	9	7	
Body weight in kg (Mean±SD)	59.9±7.93	63.15±14.54	0.387[$]
Duration of surgery in hours (Mean±SD)	2.26±0.65	1.99±0.65	0.195[$]

P values are calculated using unpaired *t*-test[$] and Chi-square test[@], SD: Standard deviation

Table 2: MRSS and NRS scores in each group

Parameter	Group C	Group F	*P* value
MRSS scores (median [IQR])	2 (1)	1 (1)	0.992
NRS scores (median [IQR])	1 (1)	4 (2)	<0.0001

P values calculated using Mann–Whitney U-test, MRSS: Modified Ramsay sedation scale, NRS: Numerical rating scale, IQR: Interquartile range

Table 3: Risk assessment for pain

Parameter	Point estimate	95% confidence interval	
		Lower limit	Upper limit
Absolute risk reduction	0.4	0.1853	0.6147
Number needed to treat	2.5	1.6268	5.3968

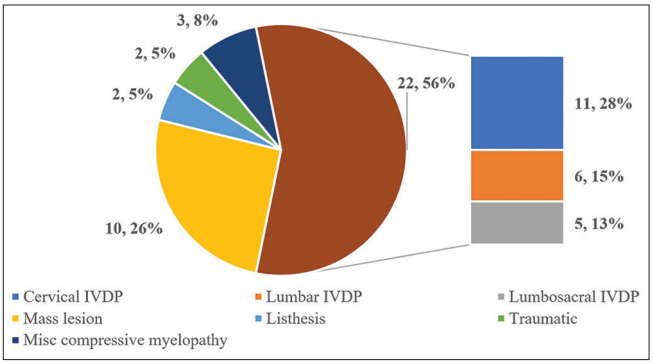

Figure 2: Diagnoses of patients undergoing spine surgeries

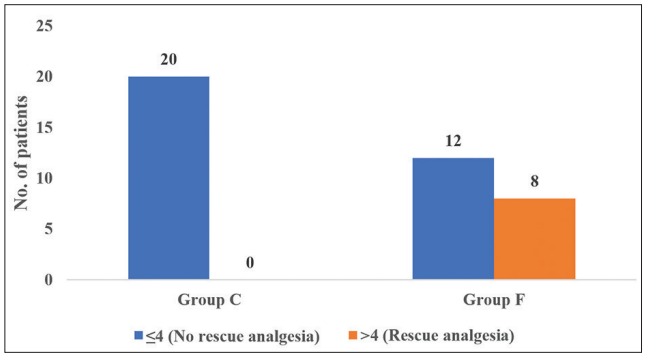

Figure 3: Numerical rating scale scores

42.33 years. The study population in the present study included 60% males and 40% females. There was no association between gender and spine abnormalities. IVDP was the most common diagnosis with cervical IVDP accounting for the most common type of IVDP. After completion of surgery, assessment of sedation using MRSS with the help of an anesthetist blinded about the study, in the immediate post-operative period, showed lesser levels of sedation in the fentanyl group than in clonidine group but this difference was not statistically significant. Pain assessment was done using NRS, the most commonly used, validated, quick and easy-to-use pain assessment scale for POP when patients are able to communicate. There was significant difference in the pain scores between the two groups. In the clonidine group, there was no requirement of rescue analgesia, unlike the fentanyl group. There were no adverse drug reactions noted perioperatively in either of the study groups.

Pain follows any surgical procedure due to cutaneous and peripheral nerve damage and tissue injury, causing local inflammation. Pain signals are transmitted by the Aδ and C fibers to the neurons in the substantia gelatinosa, which relay to the sensory cortex through the thalamus. As a protective response, descending noradrenergic pathways from locus coeruleus and dorsal raphe nucleus in the brainstem, synapse onto the neurons in substantia gelatinosa of the spinal gray matter, containing alpha-2 adrenergic receptors. As these receptors are linked to Gi subtype of G protein coupled receptor, there is opening of K+ channels, leading to neuronal hyperpolarization and inhibition of further transmission of nociceptive impulse.[5] Further, these noradrenergic neurons in the brainstem are under inhibitory control by the projections from the periaqueductal grey matter. Fentanyl, a synthetic opioid, exerts analgesic action by supraspinal and spinal effects. Supraspinally, it inhibits the inhibitory control on the descending noradrenergic tracts and promotes norepinephrine mediated inhibition of impulse transmission. In addition, it also mediates emotional component of pain by increasing the excitability of neuronal projections from dorsal raphe nucleus and locus coeruleus to the limbic forebrain. At spinal level, fentanyl through its receptors, prevents opening of voltage sensitive Ca^{2+} channels on the synaptic terminals of proximal fibres of A delta and C fibres, thus preventing neurotransmitter release and impulse transmission from presynaptic neuron to the neurons in substantia gelatinosa. Postsynaptically, there blockade of excitation of dorsal horn neurons by receptor mediated K^{+} channel opening and subsequent neuronal hyperpolarization.[6] However, fentanyl with duration of action of 20-30 minutes cannot provide postoperative analgesia for surgeries lasting for about 2 hours due to its rapid redistribution and extensive metabolism. Clonidine that is an alpha-2 adrenergic receptor agonist with duration of action of 6-24 hours, mimics the action of endogenous norepinephrine and acts directly on the alpha-2 adrenergic receptors inhibiting the firing of neurons in substantia gelatinosa that are stimulated by A delta and C fibres for a longer duration. In addition it inhibits the release of substance P y primary afferents of the dorsal horn, thus providing prolonged antinociception.[5] Further, it has also been suggested that alpha-2 adrenoceptor agonists cause release of acetyl choline in the spinal cord snd thus facilitate antinociception.[7] The age group in the present study was comparable with the study done by Prasad *et al*.[8] and the mean age in the present study wascomparable to a study done by Viswanathan *et al*.[9] There was no difference in the gender distribution between the groups, consistent with the findings of Prasad *et al*.,[8] Viswanathan *et al*.,[9] and Ganesan et al.[10] Although Miller *et al*.,[11] reported that lumbar IVDP is the most common type of IVDP and Lee,[12] and Phillips *et al*.,[13] attributed mechanical factors to be causing disc degeneration, it was seen in the present study that cervical IVDP was the most common diagnosis. This may be attributed to the degenerative changes occurring in the cervical spine starting at the third decade of life[14] and the relatively excess torsional strain experienced by cervical spine leading to increased incidence of disk prolapse in this region.[15] Sedation levels in both the study groups were comparable that was similar to the study done by Samantaray *et al*.[4] Bharti *et al*.[16] concluded that the sedation was higher in the clonidine group which is similar to the findings of this study. Locus coeruleus consists of noradrenergic neurons projecting to the cortex mediating sleep-wake cycle. Clonidine acting on alpha-2 adrenoceptors in locus coeruleus exerts a tonic inhibition on cortical arousal, thus leading to sedation.[17] POP was lesser in the clonidine group than in the fentanyl group in the present study that is akin to the study done by Bernard *et al*.[18] stating that clonidine delayed the onset of pain and hence the requirement of rescue analgesia in the post-operative period. De Kock *et al*.[19] demonstrated that intraoperative intravenous clonidine infusion resulted in better analgesia in post-operative period as compared to those who did not receive clonidine. However, the present study demonstrated that a single dose of clonidine administered as pre-anesthetic medication provides analgesia in the post-operative period, acting at spinal level and preventing central sensitization to pain.

Strengths of the present study are that it is a randomized study conducted in a tertiary care center and clonidine at the dose of 1.5 mcg/kg administered as pre-anesthetic medication proved to be an effective analgesic in the post-operative period. The limitation of the present study is that time of arousal from anesthesia was not assessed among the patients in both the study groups.

CONCLUSION

It can be concluded that premedication with intravenous clonidine 1.5 mcg/kg as an add-on to intravenous fentanyl 1 mcg/kg increases the level of sedation, decreases POP, and need for rescue analgesia in patients undergoing spine surgeries.

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