

“Effect of Continuous Low Dose Ketamine and Dexmedetomidine on Post Operative Opioid Consumption and Pain after Cervical Spine Surgery: An Observational Study”

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Abstract:

Background and Aim: Cervical spine surgery induce severe pain, that if not controlled may cause delayed recovery and longer hospital stay. Many methods and drugs are used to control postoperative pain. Present study to know the effect of continuous low dose ketamine and dexmedetomidine on fentanyl consumption and analgesic effect after cervical spine surgery.

Method: A total 62 patients of ASA I or II, aged 20-70 yrs, both sexes, scheduled for cervical spine surgery received either inj. ketamine 0.5 mg/kg bolus followed by 2 µg/kg/min infusion intraoperatively and inj. dexmedetomidine 0.5 mg/kg bolus followed by 0.3 µg/kg/hr infusion intraoperatively, that continued for 24hr postoperatively. Fentanyl was given through IV PCA postoperatively, programmed to deliver as basal infusion at the rate of 0.5 µg/kg/hr, and 0.5 µg/kg bolus on patient's demand with 6 min lockout period, for 48hr postoperatively. Pain score (VAS) was assessed at 1hr, 4hr, 8hr, 12hr, 24hr, 36hr and 48hr postoperatively. Total amount of fentanyl consumption, side effects and patient satisfaction level was assessed after 48hr postoperatively.

Result: The total amount of fentanyl consumption was found more in group D (1410.03±187.83 µg) when compared to group K (1345.70±96.20 µg) ($p>0.05$). In group K VAS score was observed lower in 1hr, 4hr, and 8hr postoperatively than in group D, which was highly significant ($p<0.05$). VAS score at 12hr, 24hr, 36hr lower in group K than group D, but that was not significant ($p>0.05$). At 48hr patients of both the groups had same VAS score. Incidence of side effects and satisfaction level was comparable in both the groups.

Conclusion: Both the study drugs, ketamine and dexmedetomidine, decreased overall fentanyl consumption and VAS score after cervical spine surgery. Both groups reduced the side effect of fentanyl and increased patient satisfaction level.

Keyword: Ketamine, Dexmedetomidine, Cervical spine surgery, IV PCA, Postoperative analgesia.

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I. Introduction

Patients presenting for cervical spine deformity correction surgery have both inflammatory and neuropathic pain related to arthritis, facet arthropathy, ligament hypertrophy, trauma and ultimately instability with the progressive development of nerve root and cord compression.¹ Postoperative pain is main factor that delayed recovery and increased hospital stay. For postoperative analgesia many drugs and methods are used. Multimodal analgesic method is the commonly used method. Commonly opioid are used for post-operative pain relief. However, there is wide inter-patients' variability in the response to opioid and significant side effects associated with its use. Patient –controlled analgesia (PCA) is commonly assumed to imply on-demand, intermittent, IV administration of opioid under patient control with or without a continuous background infusion.² Patient controlled analgesia (PCA) with opioid has been widely used for the control of post-operative pain.^{3,4}

Strong pain stimuli activate N-methyl-D-aspartate (NMDA) receptors and produce hyperexcitability of dorsal root neurons.⁵ Spinal cord hyperexcitability is involved in the pathophysiology of acute pain.⁶ This trigger induces central sensitization, the wind-up phenomenon, and pain memory.⁵ An NMDA receptor antagonist can prevent the induction of central sensitization caused by stimulation of peripheral nociception as well as by blocking the wind up phenomenon.^{5,7} Ketamine is an anaesthetic agent with N-methyl-D-aspartate (NMDA)-antagonist properties.^{6,7} Its analgesic action is due to inhibition of NMDA receptor and action on opiate receptors in the brain and spinal cord.^{7,8} Ketamine has also used in sub-anaesthetic doses as an analgesic for both acute and chronic pain relief.^{7,9} The analgesic effect of ketamine occurs at plasma concentrations between 100 and 150 ng/ml.^{9,10,11} These concentrations have been achieved by infusion as low as 2-4 µg/kg/min after

initial loading dose.^{10,11,12} Small doses of ketamine prevent central sensitization, development of acute opioid tolerance and hyperalgesia.^{5,10,13,14} Most disconcerting side effects of ketamine are its adverse psychomimetic effects, including dizziness, frightening dreams and hallucinations.

Dexmedetomidine is a selective α_2 receptors agonist and its analgesic effect is exerted both at the spinal and supraspinal levels.¹¹ Alpha-2 adrenergic receptors also act on the presynaptic membrane, inhibiting the release of norepinephrine, which in turn induces hyperpolarization and inhibits the pain signals to the brain¹⁵. Dexmedetomidine has analgesic, sedative and sympatholytic effects but without significant respiratory depression.^{4,10} Dexmedetomidine also has opioid sparing effects when used as an adjuvant for post-operative analgesia.^{4,16} Use of dexmedetomidine reduces catecholamine secretion and leads to a modest reduction in heart rate and blood pressure¹⁷, which may be particularly beneficial in patient with cardiovascular disease.¹⁶ Many studies proved that intra-operative dexmedetomidine reduces postoperative pain and opioid consumption.

II. Material and Methods

The study was conducted in department of Anaesthesia and critical care, Pt. J.N. M. Medical College and B.R.A.M. hospital Raipur, (C.G.) after approval from the institutional Scientific and Ethics committee in 62 patients who had undergone cervical spine surgeries.

Study Design: Prospective Observational study

Data collection: Prospective, pretested and preformed proforma

Study duration: April 2018 to July 2019

Study population: 62 patients

Sample size: According to previous data from **Yamauchi M et al (2008)**¹⁸, they found mean time of NSAIDs requirement for break through pain in control group 1.8 ± 1.1 and 0.6 ± 0.8 times in ketamine group.

Taking into consideration we calculated the difference between these 2 mean with confidence level 99%, type I, α error probability 0.05 in 99% power, minimum 31 samples are required for each group as compared by Epitool software.

Inclusion criteria

1. All patients undergoing cervical spine surgery at Dr B.R.A.M. Hospital & Pt. J.N.M. Medical College, Raipur (C.G.).
2. ASA physical status I or II
3. age 20-70yr

Exclusion criteria; Patients with

1. Patient refusal
2. Chronic pain syndrome
3. History of opioid and another drug abuse
4. Severe surgical area pain
5. Inability to use PCA
6. Lack of communication ability
7. Psychiatric problem
8. Hypertension
9. History of CVA
10. History of convulsion
11. Pregnancy
12. Acute and chronic renal disease or liver disease

Procedure Methodology

The present study entitled “**Effect of continuous low dose ketamine and dexmedetomidine on post-operative opioid consumption and pain after cervical spine surgery-an observational study**” was conducted in department of Anaesthesia and critical care, Pt. J.N. M. Medical College and B.R.A.M. hospital Raipur, (C.G.) after approval from the institutional Scientific and Ethics committee. After receiving approval from institutional Scientific and Ethics committee, informed and written consent about anesthetic procedure was obtained from all the patients. Patients were properly educated about the use of PCA pump. Patients aged 20-70 yrs of ASA grade I and II, who were underwent cervical spine surgeries under general anesthesia and received either intravenous low dose ketamine or dexmedetomidine as adjuvant to fentanyl at the time of skin incision. The patients were recruited for the observational analysis after allotment into two groups.

- Group D- inj. dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$ bolus and 0.3 $\mu\text{g}/\text{kg}/\text{hr}$ infusion
- Group K- inj. ketamine 0.5 mg/kg bolus and 2 $\mu\text{g}/\text{kg}/\text{min}$ infusion

All the patients had thorough pre anaesthetic evaluation, which was comprised of a detailed history, a clinical examination in either the PAC clinic or at the bedside and evaluation of the investigations.

After thorough pre-anaesthetic check-up and written informed consent, patients were taken to pre-operative preparation room. On arrival of patients into the OT, baseline ECG, pulse oximetry (SpO₂) and non-invasive blood pressure (NIBP) were recorded using Philips MP30 monitor. Intravenous line was established and Infusion of 500 ml Lactated Ringer’s solution was given. All patients were premedicated with IV ondansetron 4mg and ranitidine 50 mg. Anesthesia was induced with propofol 2-3 mg/kg and fentanyl 2 µg/kg and endotracheal intubation was facilitated with inj. atracurium. Anesthesia was maintained with isoflurane 1-3% and nitrous oxide 60% in oxygen and muscle relaxation was achieved with inj atracurium. In ketamine group bolus ketamine 0.5 mg/kg followed by continuous ketamine 2 µg/kg/min for 24hr. Continuous ketamine infusion was given at the skin incision intra-operatively and that was continued till 24hr postoperatively. In dexmedetomidine group bolus dexmedetomidine 0.5 µg/kg followed by continuous dexmedetomidine 0.3 µg/kg/hr for 24hr postoperatively. Glycopyrrolate 0.02 mg/kg and neostigmine 0.05 mg/kg was used for reversal of residual muscle relaxant. Patients were extubated after full consciousness was gained and shifted to postoperative room and monitored.

For the post-operative pain control fentanyl using IV PCA was given. In recovery room IV PCA containing fentanyl was attached. PCA was programmed to deliver 0.5 µg/kg/hr of fentanyl on basal infusion for 48 hr and 0.5 µg/kg on demand with 6 min lockout period. The total amount of fentanyl consumption, post-operative pain score, patient’s satisfaction and side effects were evaluated after 48hr. Post operatively pain was evaluated by visual analogue score (VAS score) in 1hr, 4hr, 8hr, 12hr, 24hr and 48hr after surgery. Data were collected from all the patients and observations were analysed and compared

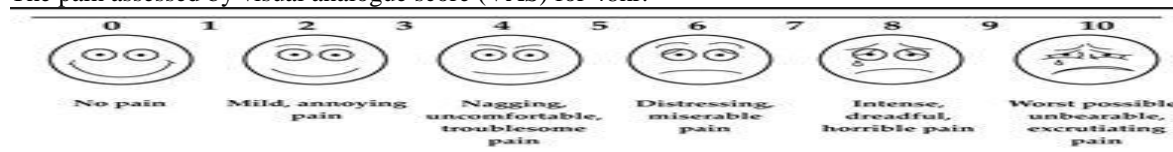
Clinical data:

Heart Rate (HR)

Systolic blood pressure (SBP)

Diastolic blood pressure (DBP)

The pain assessed by visual analogue score (VAS) for 48hr.



Amount of fentanyl consumption

Patient satisfaction level (very satisfied-5, satisfied 4, neutral 3, dissatisfied 2, very dissatisfied 1)

Side effects (nausea, vomiting, headache, sedation and hallucination)

III. Results

Distribution of patients according to ASA grade was comparable in both groups. The mean age of patients in group K and group D was 46.22±9.7yr and 44.41±9.02 respectively (p=0.449). Minimum age was 20yr and maximum age was 62yr in our study. Distribution of patients according to the age in the both groups were statistically comparable (p>0.05). Male: female in group K was 24:7 and in group D was 23:8. The distribution of patients according to the sex was statistically comparable between the groups. Mean weight of patients in group K 66.12±7.75 kg where as in group D 62.61±7.50 kg, (p=0.07). The weight wise distribution of the patients was comparable within the groups.

Mean duration of surgery in group K and group D was 4.93±0.89hr and 5.06±0.89hr, respectively and the difference was statistically comparable (p=0.567).

HEMODYNAMICS PARAMETERS

Mean Heart rate

In our study,HR was observed lower as compared to the baseline HR within the group and difference was statistically insignificant in group K (p>0.5) and significant in group D (p<0.05). Mean HR of group D was lower as compared to group K at all measured time and the difference was statistically insignificant (p>0.05).

Mean systolic blood pressure

The difference in mean SBP in the observational period of both the groups was statistically not significant at any given time during the postoperative period (p>0.05). In group D mean SBP noted lower than the baseline SBP in all measured duration, which was statistically significant (p<0.05).

Mean diastolic blood pressure

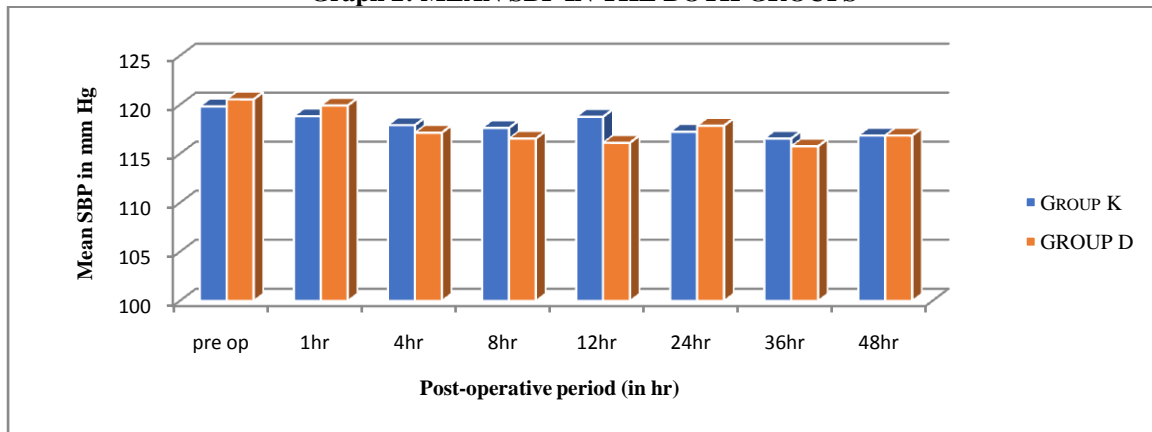
Mean DBP of group K was found higher than the group D post operatively, but it was statistically not significant ($p>0.05$). Mean DBP in patients of group D was observed significantly lower in 1hr, 4hr, 8hr, 12hr, 24hr, 36hr, and 48hr, as compared to baseline DBP, ($p<0.001$) and it was statistically significant($p<0.05$).

Graph 1: MEAN HEART RATE (HR) (bpm) in the both groups



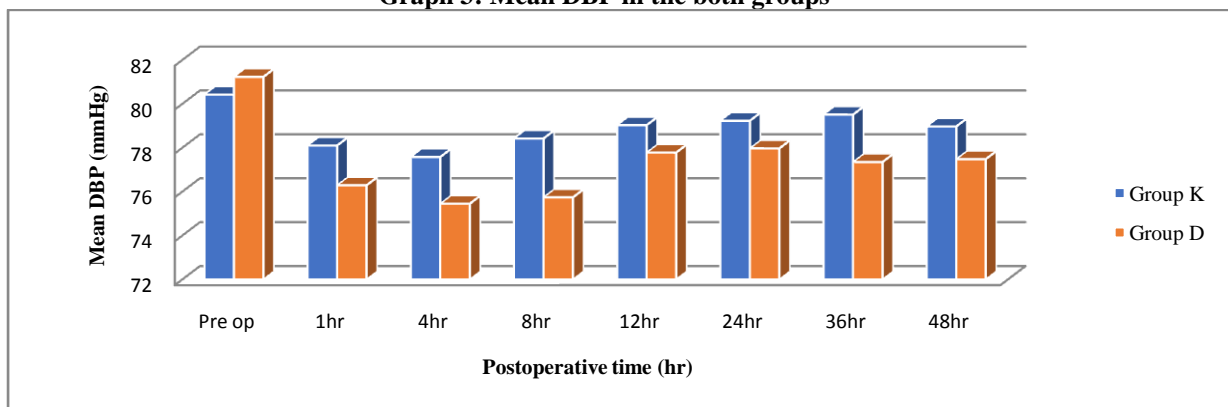
Graph 1 shows variations in mean HR at various time interval in both the groups.

Graph 2: MEAN SBP IN THE BOTH GROUPS



Graph 2 shows mean SBP in the both groups in various times.

Graph 3: Mean DBP in the both groups



Graph 3 shows mean DBP in the both groups in all measured time.

Total amount of fentanyl consumed

We found demand was more in group D as compared to group K and total amount of fentanyl consumption was more in group D ($1410.03 \pm 187.83 \mu\text{g}$) than the group K ($1345.70 \pm 96.20 \mu\text{g}$), which was found statistically insignificant ($p=0.094$).

Pain score (VAS score)

Preoperative pain score VAS 5.2±0.81 in group K and 5.41±0.62 in group D (p=0.25). In group K VAS score was observed lower in 1hr, 4hr, and 8hr postoperatively than in group D, which was found statistically highly significant (p<0.05). VAS score at 12hr, 24hr, 36hr lower in group K than group D, but that was not significant (p>0.05). At 48hr patients of both the groups had same VAS score.

Table 1: Painscore (VAS) in the both groups

VAS	Group K	Group D	P value
pre- op	5.2±0.81	5.41±0.62	0.25
Post- op			
1hr	3.94±0.72	4.3±0.59	0.03
4hr	2.75±0.85	3.21±0.61	0.016
8hr	1.5±0.85	2.12±0.72	0.003
12hr	0.64±0.66	0.90±0.63	0.117
24hr	0.19±0.40	0.25±0.44	0.57
36hr	0.06±0.24	0.096±0.30	0.60
48hr	0.032±0.17	0.032±0.17	1

Table shows pain score (VAS) in the both groups in various times.

Table 2: Side effects in the both groups

Side effects	Group K (No of patients)	Group D (No of patients)	P value
Nausea	4	4	1
Vomiting	1	0	0.31
Headache	1	1	1
Sedation	1	3	0.30
Hallucination	1	0	0.31

Table 3: Satisfaction level in both groups

Satisfaction level	Group K	Group D	P value
Very satisfied	3	5	0.45
Satisfied	23	19	0.28
Neutral	5	7	0.52
Dissatisfied	0	0	
Very dissatisfied	0	0	

III. Discussion

In our study, the baseline Heart rate (HR) in group K and group D was 76.48±7.59 beats per minute (bpm) and 75.29±7.53 bpm respectively and difference was statistically not significant (p=0.52). In both groups HR was observed lower when compared to the baseline HR within the group and the difference was statistically comparable in group K (p>0.5) and significant in group D (p<0.05), but there was no requirement of atropine. The difference of HR in group D was due to dexmedetomidine which causes dose-dependent decreases in heart rate and blood pressure, concomitant with decreasing plasma catecholamines.^{10,16,17} Mean HR of group D was lower as compared to group K at all measured time and the difference was statistically insignificant (p>0.05). But all patients were hemodynamically stable during the study period. **Garg N et al (2015)**¹⁹ and **Du J et al (2018)**²⁰ found patients hemodynamically stable during the study period, result was comparable to our study but here, there was no significant decrease in heart rate in spite of use of dexmedetomidine at same doses. **Zhang B et al (2017)**⁴ found heart rate in dexmedetomidine group was statistically decreased from baseline HR for over 20 min after arriving at the PACU (p<0.05), result was similar to our study but our patients were stable during study period. Though their time of delivery of dexmedetomidine was after extubation. **Mitra R et al (2017)**¹⁴ found average HR and MAP was significantly increased during initial 30-45 min of surgery in ketamine group just after giving bolus of drug and starting of infusion. To avoid hemodynamic side effects, we used low dose of dexmedetomidine (loading dose 0.5 µg/kg followed by 0.3 µg/kg/hr). Ketamine produces an increase in HR, BP and stroke volume. These effects peak in 2 min after IV administration and settle within 15-20 min and are also dose dependent. To avoid these effects in our study we used low dose ketamine (0.5 mg/kg loading dose followed by 2 µg/kg/min).

In our study, patients were given fentanyl 2 µg/kg IV during induction and through IV PCA postoperatively, programmed to deliver 0.5 µg/kg/hr as basal infusion and 0.5 µg/kg bolus on patient demand with 6 min lockout period. We found demand was more in group D as compared to group K and the total amount of fentanyl consumption was more in the group D (1410.03±187.83 µg) than the group K (1345.70±96.20 µg), which was found statistically insignificant (p=0.094).

As per the total consumption of opioid, our study was comparable to the study by **Garg N et al (2015)**¹⁹ who found rescue morphine requirement was comparable in ketamine and dexmedetomidine group (7.98±7.724 mg for group D and 2.59 ±1.974 mg for group K [p<0.05]). Ketamine has analgesic properties that

are mediated by number of mechanisms, mainly by acting on NMDA receptor²¹. Addition of low dose ketamine to opioids produces synergistic or an additive analgesic effect most likely as a result of the combination of presynaptic opioid inhibition reducing afferent transmission by diminished transmitter release and postsynaptic NMDA blockade which reduces wind up and central sensitization¹². Dexmedetomidine is a potent α_2 adrenoreceptor agonist with α_1 : α_2 selectivity ratio of 1:1600 and it has sedative, anxiolytic, anesthetic sparing effect. It can enhance the analgesia produced by opioid and reduces the requirement of opioid^{4,10}.

In our study, pain was assessed by the use of VAS score at 1hr, 4hr, 8hr, 12hr, 24hr, 36hr and 48hr postoperatively. Preoperative pain score VAS 5.2 ± 0.81 in group K and 5.41 ± 0.62 in group D which was statistically comparable in the both groups ($p=0.25$). In group K, VAS score observed was lower in 1hr, 4hr, and 8hr postoperatively than in group D, which was highly significant ($p<0.05$). VAS score at 12hr, 24hr, 36hr was lower in group K than group D, but that was not significant ($p>0.05$). At 48hr patients of both the groups had same VAS score. As per the pain score (VAS), our study was comparable with studies **Garg N et al (2015)**¹⁹ and **Mitra R et al (2017)**¹⁴. Ketamine produce dissociative anesthesia and analgesia. Ketamine is an anaesthetic agent with N-methyl-D-aspartate (NMDA)-antagonistic properties.^{6,7} Its analgesic action is due to inhibition of NMDA receptor and action on opiate receptors in the brain and spinal cord.^{7,18} It has been reported that ketamine enhances analgesic effect of opioid and reduces the incidence of side effects and development of tolerance. **Javery KB et al (1995)**¹¹, **Yamauchi M et al (2008)**¹⁸, and **Kaur S et al (2015)**²³ observed that ketamine reduces pain score. **Burstal R et al (2001)**²⁴, **Kim SH et al (2013)**¹², **Naik B I et al (2016)**¹, found pain score of the study drugs was comparable to the control group. The difference might be because of **Burstal R et al (2001)**²⁴ had done study on women, **Kim SH et al (2013)**¹² had compared two different dose of the ketamine, and **Naik BI et al (2016)**¹ had done study to compare postoperative pain after multilevel spine surgery.

In our study, side effect such as nausea, vomiting, headache, sedation and hallucination were observed during postoperative period in measured time interval and data was collected and analysed after 48 hr. Nausea was experienced by equal number of patients in both the groups. Vomiting was experienced by 1 patient of group K vs. none of the patients in group D ($p=0.31$). Headache experienced by 1 patient of both the groups. 3 patients were found sedated in the group D whereas 1 patient in group K ($p=0.30$). Hallucination was experienced by 1 patient of group K whereas no patient of the group D experienced the same. Incidence of side effects were found statistically not significant in both the groups. As per incidence of side effects, our study was comparable to other studies **Javery KB et al (1995)**¹¹, **Kim SH et al (2013)**¹², **Kaur S et al (2015)**²³, **Mirkheshti A et al (2017)**³, **Zhang B et al (2017)**⁴. Ketamine and dexmedetomidine both decrease the opioid requirements; thus, it decrease side effects of opioid.

In our study, the level of satisfaction (5, very satisfied; 4, satisfied; 3, neutral; 2, dissatisfied; 1, very dissatisfied) was assessed after 48 hr postoperatively. 3 patients of group K and 5 patients of group D were very satisfied ($p=0.45$). 23 patients of group K and 19 patients were satisfied ($p=0.28$). 5 patients of group K and 7 patients of group D were neutral to their pain relief, which was statistically comparable in the both groups. **Zhang B et al (2017)**⁴ and **Du J et al (2018)**²⁰ observed satisfaction with pain control was statistically higher in dexmedetomidine group than in control group ($p<0.05$). **Mitra R et al (2017)**¹⁴ found that, hospital stay of patients was least in ketamine group when compared with group dexmedetomidine and saline group ($p=0.09$).

IV. Conclusion

In our study we found that, both the study drugs, ketamine and dexmedetomidine decreased the total fentanyl consumption and pain score after the cervical spine surgery, meanwhile we also compared that ketamine had better effect on reduction of total fentanyl consumption and pain score. Both groups reduced the side effects of fentanyl and increased the satisfaction level.

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