Hemodynamic Responses at Intubation, Change of Position, and Skin Incision: A Comparison of Multimodal Analgesia with Conventional Analgesic Regime

Keelara Shivalingaiah Savitha, Radhika Dhanpal, M. S. Vikram
Department of Anaesthesia, St. John’s Medical College Hospital, Bengaluru, Karnataka, India

Abstract

Background: Lumbar spine surgery is associated with hemodynamic variations at intubation, change of position, and skin incision. A balanced anesthesia with multimodal analgesia (MMA) is necessary to attenuate these changes. Aim: To assess the relative effectiveness of preemptive MMA compared with the conventional analgesic regime in suppressing the hemodynamic response to endotracheal intubation, prone positioning, and skin incision. Settings and Design: A randomized, prospective study involving 42 patients belonging to the American Society of Anesthesiologists Physical Status I and II scheduled to undergo elective lumbar spine surgery were allocated into two groups of 21 each. Materials and Methods: Forty-two patients were randomly allocated into Groups A and B. Group A (study group) received diclofenac, paracetamol, clonidine, and bupivacaine with adrenaline skin infiltration and Group B (control group) injection paracetamol and saline with adrenaline skin infiltration. Statistical Analysis Used: Hemodynamic parameters (heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP], and mean arterial pressure [MAP]) between the groups following intubation, prone position, and skin incision were noted and compared using repeated measure analysis of variance. One sample t-test was used to compare the standard mean concentration with the means of the study and control groups. P < 5% being considered statistically significant. Results: In the study group, HR, SBP, DBP, and MAP were lower at intubation and change of position as compared to the control group and were statistically significant. Conclusion: Preemptive MMA with balanced anesthesia is effective in attenuating the hemodynamic responses to multiple noxious stimuli during lumbar spine surgery.

Keywords: Balanced anesthesia, hemodynamic parameters, intubation, lumbar spine surgery, multimodal analgesia, prone position, skin incision

INTRODUCTION

In the current clinical practice, balanced anesthesia is preferred to achieve adequate depth rather than deepening the planes of anesthesia with volatile agents. It is an established fact that balanced anesthesia has four components: Analgesia (antinociceptive), amnesia (hypnotic), muscle relaxation, and abolition of autonomic reflexes. Imbalance in any one of the components leads to stress response (autonomic, endocrine, metabolic, and immunological responses) to a noxious stimulus which delays wound healing. In susceptible patients, it may lead to organ dysfunction such as myocardial ischemia and infarction. To surmount the stress response, it is not feasible to maintain deeper plane of anesthesia with volatile agents alone throughout the procedure as this results in hemodynamic instability and also does not ensure adequate analgesia.

In balanced anesthesia, hypnotic and antinociceptive components are interconnected. A strong antinociceptive component reduces hypnotic requirement and vice versa. To have intense analgesia, multimodal analgesia (MMA) is the scientific approach to treat acute pain with least side effects. The concept of MMA was introduced in 1990s to fast track recovery; later, it was considered for better recovery.
postoperative analgesia.\textsuperscript{[11,12]} It targets all four elements of pain processing: (1) Transduction, (2) transmission, (3) modulation, and (4) perception,\textsuperscript{[13]} whereas in the conventional regime, only one or two elements are targeted.

The present study was designed to assess the intensity of analgesia with the bolus doses of preemptive MMA drugs compared with conventional analgesic regime, for a series of noxious stimuli, with varied intensity such as endotracheal intubation, prone position, and skin incision (action points). They are the most intense stimuli which precede stress response during the surgical procedure in patients undergoing lumbar spine surgery. In the study, preemptive analgesia was considered to prevent nervous system sensitization.\textsuperscript{[14]}

The study tested the hypothesis that preemptive MMA modulates the cardiovascular response to action points in patients undergoing lumbar spine surgery and is the first of its kind.

\section*{Materials and Methods}

This randomized, prospective double-blind clinical study was carried out in a tertiary care center after obtaining the Institutional Review Board approval and informed written consent from the patients. Forty-two patients scheduled for lumbar spine surgery between 20 and 65 years, of both sex, with body mass index of 18–30 belonging to the American Society of Anesthesiologists Physical Status I and II were included in the study. Pregnant women, patients with bronchial asthma, and known drug allergy were excluded from the study. Patients were randomly allocated into two groups ($n=21$), Group A and Group B by allocation sequence generated by computer-generated random number table.

Confirming the preanesthetic evaluation and consent, the following monitors were connected in the induction room: Electrocardiogram, noninvasive blood pressure, $O_2$ saturation of hemoglobin, bispectral index (BIS), and train of four (TOF, neuromuscular monitor) for monitoring throughout the surgery. For drug and fluid administration intravenous access was secured. Patients were oxygenated during the study drug administration by $O_2$ mask. All patients received midazolam 0.03 mg/kg, ondansetron 4 mg, and glycopyrrolate 0.2 mg intravenously. The study drugs were prepared by assigned postgraduate students who were not participating in the study. Analgesic drugs were administered preemptively before induction providing sufficient time for the onset of action. Group A: (study group/MMA group) Received diclofenac sodium, paracetamol and clonidine intravenously, and local skin infiltration (bupivacaine with adrenaline). Group B: (control group/conventional regime group) Received paracetamol and local skin infiltration (saline with adrenaline). Following the study drug administration, patients were preoxygenated with 100\% $O_2$, 5 L/min for 3 min. Fentanyl 3 $\mu$g/kg was given to all patients 2 min before induction with propofol, followed by atracurium 0.5 mg/kg to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane in 60\% $N_2O$ and $O_2$, atracurium, and morphine. Heart rate (HR) and blood pressure (BP) were maintained within $\pm$ 10\% of the baseline values intraoperatively. End tidal $CO_2$ and end-tidal isoflurane concentration were continuously monitored using an infrared gas analyzer. The minimum alveolar concentration (MAC) of isoflurane was titrated to achieve BIS of 50–55 throughout the surgery. At the conclusion of surgery, all patients were allowed to recover spontaneously to TOF $T_1$. Residual neuromuscular blockade was reversed with glycopyrrolate 10 $\mu$g/kg and neostigmine 50 $\mu$g/kg administered intravenously. Tracheal extubation was done when the following criteria were met: BIS: 85–88 and TOF $T_1/T_0$ ratio $\geq$ 0.9. For statistical analysis, HR, systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) just before action points and 1 min, and 2 min following action points were considered.

Adverse effects of analgesic drugs such as intraoperative bradycardia (opioid, clonidine) bronchospasm, gastritis (nonsteroidal anti-inflammatory drugs), postoperative nausea, vomiting, and respiratory depression (opioid) were noted.

\section*{Statistics}

This study was nested within a study whose objective was to assess “the effect of multimodal perioperative analgesia on stress response to surgery and on postoperative pain score” in patients undergoing lumbar spine surgery. Normally, distributed data of HR, SBP, DBP, and MAP for endotracheal intubation, change of position, and skin incision between the two groups (study group and control) were presented as mean $\pm$ standard deviation and were compared using repeated measure the analysis of variance. One sample t-test was used to compare the standard mean concentration with the means of the study and control groups, $P < 5\%$ being considered statistically significant. Data were analyzed using SPSS software (SPSS Inc., Release 2009. PASW Statistics for Windows, Version 18.0, Chicago, IL, USA).

\section*{Results}

The demographic data were comparable in both the groups. In the study group, HR at all action points was significantly lower from 0 min to 2 min, except at 2 min following skin incision, $P = 0.314^a$ [Table 1 and Figure 1]. In the study group, SBP, DBP, and MAP were significantly lower following endotracheal intubation and change of position. However, following skin incision, there was no statistical difference between the groups [Tables 2-4 and Figures 2-4]. Postextubation no adverse effects were noted in the study group, however, in the control group, majority of the patients had nausea and few had vomiting.

\section*{Discussion}

The aim of the study was to assess the relative effectiveness of preemptive MMA compared with conventional analgesic regime in suppressing the hemodynamic response to endotracheal intubation, prone position, and skin incision. In the present study, a series of stressors were considered because with inadequate analgesia repetitive noxious
stirnus has adverse effect on all organ system. In clinical anesthesia, as there is no specific indicator for nociceptive-antinociceptive balance, anesthesiologists use isolated nonspecific autonomic responses (HR and BP) as the end points in anesthetizing surgical patients. Laryngoscopy and endotracheal intubation are an integral part of general anesthesia to secure the airway, whereas change of position (prone position) and skin incision are the requirements for surgical access.

Channaiah et al. studied the efficacy of fentanyl on intubation response. They found 15% reduction in the HR compared to control group which was statistically significant \((P \leq 0.001)\). In the present study, fentanyl was included because of its rapid onset of action, high potency, and hemodynamic stability.\(^1\) Arora et al. in their study found HR of 83.77 ± 16.31 beats per min (bpm) at 1 min following intubation in patients who received clonidine with fentanyl; whereas in patients who received only fentanyl, the HR was 96.97 ± 11.47 bpm. They concluded that clonidine with fentanyl is better than fentanyl alone because clonidine is a powerful sedative and analgesic and also inhibits the release of catecholamines.\(^1^,1^7,1^8\)

In accordance with their findings, in the present study, HR was significantly low in the MMA group at 1 and 2 min following intubation \( (P = 0.002^b \text{ and } P < 0.01^b \) respectively, \([\text{Table 1}]\). At 1 min following intubation, HR was 100.62 ± 24.55 bpm in the control group where as in the study group, it was 86.71 ± 11.136 bpm. This shows that clonidine with fentanyl is a good combination in suppressing hemodynamic response to endotracheal intubation. Channaiah et al. found significant attenuation of SBP, DBP, and MAP (12.4%, 9.4%, and 11.3%, respectively) with fentanyl.\(^1^6\) However, Arora et al. found increase in SBP by 13.23%, DBP by 9.42%, and MAP by 12.78% from baseline value with only fentanyl as compared to fentanyl with clonidine.\(^1^7\) In the present study, at 1 min following intubation, in the MMA group, SBP, DBP, and MAP were significantly low \((P < 0.001^b, \ P = 0.023^b, \text{ and } P < 0.001^b \) respectively). This shows that a combination of drugs inhibits conduction in the pain pathway at various levels and attenuates hemodynamic response to intubation better than a single drug.

![Figure 1: Comparison of heart rate between time points (repeated measure analysis of variance time*group interaction test used)](image)

### Table 1: Comparison of heat rate (bpm) between the control group and the study group

| Time (min) | Control group (mean±SD) | Study group (mean±SD) | P |
|-----------|-------------------------|-----------------------|---|
|           | Intubation | Change of position | Skin incision | Intubation | Change of position | Skin incision |     |
| 0 (just before action points) | 75.57±16.042 | 79.38±15.032 | 76.76±13.605 | 78.19±12.436 | 71.24±10.440 | 70.48±9.616 | 0.002^a |
| 1 min following action points | 100.62±24.555 | 96.76±12.087 | 86.67±18.717 | 86.71±11.136 | 80.19±15.845 | 71.67±12.555 |     |
| Difference between 1 min and 0 min | 25.05±21.491 | 17.38±9.912 | 9.90±8.910 | 8.52±6.750 | 8.95±9.135 | 1.19±6.743 | 0.002^b, 0.007^c, 0.001^d |
| 2 min following action points | 100.67±24.945 | 91.57±12.052 | 81.33±16.605 | 81.67±11.569 | 75.57±15.253 | 72.76±11.158 |     |
| Difference between 2 min and 0 min | 25.10±21.790 | 12.19±10.838 | 4.57±8.322 | 8.48±7.474 | 4.33±7.255 | 2.29±6.018 | <0.01^b, 0.009^c, 0.314^d |

Statistically significant at \(P<0.05 \text{ and } 95\% \text{ CI. Action points: } \text{Intubation, change of position and skin incision. RMANOVA test and one sample } t\text{-test used.}^a\) Comparison of HR at 0 min between control group and study group. Comparison of difference in HR at 1 min and 2 min from 0 min at *intubation, 'change of position and 'skin incision between control group and study group. SD=Standard deviation, HR=Heart rate, RMANOVA=Repeated measure analysis of variance, CI=Confidence level, bpm=Beats per minute
Table 2: Comparison of systolic blood pressure (mmHg) between control group and study group

| Time (min)                      | Control group (mean±SD) | Study group (mean±SD) | P       |
|--------------------------------|-------------------------|-----------------------|---------|
|                                | Intubation              | Change of position    | Skin incision | |
| 0 min (just before action      | 101.62±14.158           | 106.95±13.377         | 108.52±12.956| 104.10±15.665 | 103.62±10.952 | 102.33±9.415 | 0.193   |
| points)                        |                         |                      |          |                  |                  |          |         |
| 1 min following action points  | 159.29±22.712           | 134.81±18.479         | 121.95±15.769| 128.38±19.320 | 117.76±17.309 | 107.57±15.194|          |
|                                |                         |                      |          |                  |                  |          |         |
| Difference between 1 min       | 57.67±16.686           | 27.86±20.783          | 13.43±16.222| 24.29±17.298   | 14.14±16.545   | 5.24±11.700  | <0.001  |
| and 0 min                      |                         |                      |          |                  |                  |          |         |
| 2 min following action points  | 141.00±19.870           | 132.00±14.381         | 117.67±15.091| 119.76±20.911 | 114.67±18.583 | 107.14±14.565|          |
|                                |                         |                      |          |                  |                  |          |         |
| Difference between 2 min       | 39.38±20.64            | 25.05±20.738          | 9.14±15.064 | 15.67±17.576   | 11.05±17.203   | 4.81±10.633  | <0.001  |
| and 0 min                      |                         |                      |          |                  |                  |          |         |

Statistically significant at P<0.05 and 95% CI. Action points: Intubation, change of position and skin incision. RMANOVA test and one sample t-test used.

Comparison of SBP at 0 min between control group and study group. Comparison of difference in SBP at 1 min and 2 min from 0 min at *intubation, change of position and skin incision between control group and study group. SD=Standard deviation, SBP=Systolic blood pressure, RMANOVA=Repeated measure analysis of variance, CI=Confidence level

Table 3: Comparison of diastolic blood pressure (mmHg) between control group and study group

| Time (min)                      | Control group (mean±SD) | Study group (mean±SD) | P       |
|--------------------------------|-------------------------|-----------------------|---------|
|                                | Intubation              | Change of position    | Skin incision | |
| 0 min (just before action      | 64.81±11.652            | 65.37±7.933           | 68.14±8.923 | 63.33±12.411 | 64.81±13.348 | 64.43±14.119| 0.681   |
| points)                        |                         |                      |          |                  |                  |          |         |
| 1 min following action points  | 94.29±17.295            | 86.29±14.181          | 76.05±9.708 | 79.90±13.935 | 74.67±15.206 | 67.48±16.681|          |
|                                |                         |                      |          |                  |                  |          |         |
| Difference between 1 min       | 29.48±19.317            | 20.90±15.909          | 7.90±11.987| 16.57±15.832   | 9.86±9.769    | 3.05±8.857  | 0.023   |
| and 0 min                      |                         |                      |          |                  |                  |          |         |
| 2 min following action points  | 85.86±15.973            | 81.38±14.928          | 75.38±8.980| 71.52±16.148   | 70.76±18.652 | 67.00±17.390|          |
|                                |                         |                      |          |                  |                  |          |         |
| Difference between 2 min       | 21.05±21.103            | 16.00±16.389          | 7.24±11.379| 8.19±13.786   | 5.95±11.535   | 2.57±7.857  | 0.025   |
| and 0 min                      |                         |                      |          |                  |                  |          |         |

Statistically significant at P<0.05 and 95% CI. Action points: Intubation, change of position and skin incision. RMANOVA test and one sample t-test used.

Comparison of DBP at 0 min between control group and study group. Comparison of difference in DBP at 1 min and 2 min from 0 min at *intubation, change of position and skin incision between control group and study group. SD=Standard deviation, DBP=Diastolic blood pressure, RMANOVA=Repeated measure analysis of variance, CI=Confidence level

Table 4: Comparison of mean arterial pressure (mmHg) between control group and study group

| Time (min)                      | Control group (mean±SD) | Study group (mean±SD) | P       |
|--------------------------------|-------------------------|-----------------------|---------|
|                                | Intubation              | Change of position    | Skin incision | |
| 0 min (just before action      | 76.05±12.890            | 79.67±10.603          | 80.86±8.552 | 76.14±12.772 | 75.76±11.777 | 75.67±11.115| 0.389   |
| points)                        |                         |                      |          |                  |                  |          |         |
| 1 min following action points  | 116.19±18.332           | 102.33±15.759         | 89.62±11.851| 95.71±15.496   | 87.57±16.436   | 80.14±15.493|          |
|                                |                         |                      |          |                  |                  |          |         |
| Difference between 1 min       | 40.14±14.864            | 22.67±16.989          | 8.76±11.379| 19.57±18.627   | 11.81±13.083   | 4.48±11.147| <0.001  |
| and 0 min                      |                         |                      |          |                  |                  |          |         |
| 2 min following action points  | 108.81±16.409           | 98.52±15.184          | 88.19±10.624| 88.05±15.794   | 84.43±18.659  | 80.24±14.943|          |
|                                |                         |                      |          |                  |                  |          |         |
| Difference between 2 min       | 32.76±18.721            | 18.86±21.692          | 7.33±10.175| 11.90±15.566   | 8.67±13.533   | 4.57±10.534| <0.001  |
| and 0 min                      |                         |                      |          |                  |                  |          |         |

Statistically significant at P<0.05 and 95% CI. Action points: Intubation, change of position and skin incision. RMANOVA test and one sample t-test used.

Comparison of MAP at 0 min between control group and study group. Comparison of difference in MAP at 1 min and 2 min from 0 min at *intubation, change of position and skin incision between control group and study group. SD=Standard deviation, MAP=Mean arterial pressure, RMANOVA=Repeated measure analysis of variance, CI=Confidence level

Wadsworth et al. did a study on four different types of prone positioning on cardiovascular parameters in healthy unanesthetized volunteers and have concluded that prone position itself may not alter HR and MAP. They have stated that exaggerated hemodynamic response may occur in anesthetized state.[19] In literature, there are studies in prone patients on cardio dynamics where the focus was on pulse pressure variation and stroke volume variation to predict...
Whereas in the present study, hemodynamic response immediately after turning the patients prone was assessed with MMA drugs, which is the first of its kind.

Channabasappa and Shankarnarayan in their study on hemodynamic changes between the prone and supine extubation in patients undergoing lumbar disc surgery found a significant rise in the HR and MAP in patients’ extubated in the supine position. The maximum increase in HR was 7.4 ± 2.7 bpm in patients extubated prone and 32 ± 3.7 bpm in patients extubated supine. Similarly, rise in MAP was 7.8 ± 2.2 mmHg in patients extubated prone and 15.2 ± 2.3 mmHg in patients extubated supine. In the present study, hemodynamic response following prone positioning was significantly low in the study groups compared to control group [HR - Table 1, SBP - Table 2, DBP - Table 3, and MAP - Table 4]. Rise in HR was 4.33 ± 7.255 bpm and MAP was 8.67 ± 13.533 mmHg in the study group, whereas it was 12.19 ± 10.838 bpm and 18.86 ± 21.69 mmHg, respectively in the control group, at 2 min following prone positioning. The only difference between the studies was, in the present study hemodynamic changes following positioning the patients prone for the surgery was assessed, whereas in Channabasappa’s study hemodynamic changes at the conclusion of the surgery following turning the patients supine till extubation was considered. The inference was that ETT in situ causes reflex hemodynamic response at the time of change of position. In the present study, hemodynamic response after turning the patients, prone was minimal in the MMA group due to intense analgesia; whereas in Channabasappa’s study, it was due to least handling of the airway, where even suctioning was not done at the time of extubation in prone position.

Elimination of somatic and autonomic response to skin incision are the clinical end-points for assessing the depth of anesthesia which is a well-known fact. To attenuate the
hemodynamic response to skin incision, different modalities have been used. Katoh et al. found sevoflurane as a sole agent did not prevent cardiovascular responses to skin incision at clinical concentrations (1–2 MAC) and was associated with the risk of excessive hypotension. In addition, they found marked reduction in MAC and MAC-BAR of sevoflurane with low concentration of fentanyl (1 and 3 ng/mL) and N_2O; whereas with increasing concentration of fentanyl (6 ng/mL), they observed ceiling effect.[23] The inference is that sevoflurane would be safer and more effective when used with a combination of drugs. Johansen et al. studied the effect of esmolol on propofol requirement for skin incision. They found no significant change in propofol requirement in low-dose infusion group compared to control group. In high-dose infusion group, it was reduced by 26% which was supposed to be 50% reduction based on computer-assisted continuous infusion target.[24] This clarifies that escalating the dose of a drug will not exponentially increase its clinical efficacy. Rantanen et al. based on clinical signs, intensity of the stimulus and serum level of analgesic drugs, derived a tool, the clinical signs-stimulus-antinociception score to estimate nociception at the time of skin incision. They recorded physiological response to skin incision at 3 different target control infusion (TCI) levels of remifentanil (1, 3 and 5 ng/mL), and they derived an indicator of nociception: Response index of nociception. They concluded that the hemodynamic response to a large incision with lower TCI of remifentanil 1 ng/mL was more marked than to a small incision with TCI of remifentanil 3 or 5 ng/mL.[10] This reveals that intense analgesia is a must for major surgeries which can be achieved with MMA. Johansen et al. found a significant increase in the HR and MAP after endotracheal intubation but not after skin incision.[24] Accordingly, in the present study, following skin incision, hemodynamic parameters between the groups were not statistically significant. This shows that intubation and change of position need deeper plane of anesthesia (Stage III, Plane III and IV) compared to skin incision (Stage III, Plane II and III) which can be accomplished only by MMA.

The end results of the above-mentioned studies states that higher doses of drug may end up with ceiling effect or may not be clinically effective as a sole agent to completely inhibit stress response to noxious stimuli. With small doses of study drugs, the clinical effect may not be statistically significant when compared with the control group. In brief, MMA drugs interact synergistically and provide intense analgesia. It also improves hemodynamic stability before and after noxious stimuli during the course of surgery. Further studies are necessary with MMA to motivate the clinicians with evidence-based literature and to improve the quality of perioperative pain management which is still far from satisfactory.

**Conclusion**

Under general anesthesia, a nociceptive-antinociceptive balance is established which is enhanced by MMA for a given noxious stimulus because of additive analgesic effects. It is more robust as compared to conventional analgesic regime in anesthetized, paralyzed patients during the course of the surgery. This shows that balanced anesthesia with MMA can be recommended to suppress the hemodynamic response to varied intensity of surgical stimuli.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Fukuda K. Opioid analgesics. In: Miller RD, Cohen NH, Erikssson LI, Fleisher LA, Wiener-Kronish JP, Young WL, editors. Miller’s Anesthesia. 8th ed. Philadelphia: Elsevier Saunders; 2015. p. 864-914.

2. Evers AS, Crowder M. Mechanisms of anaesthesia and consciousness. In: Barash PG, Cullen BF, Stoelting RK, Cahalan MK, stock MC, editors. Clinical Anaesthesia. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2009. p. 95-114.
3. Singh M. Stress response and anaesthesia. Altering the peri and post-operative management. Indian J Anaesth 2003;47:427-34.
4. Hopf HW, Cochran CR, Dorough MB, Dull RO. Inflammation, wound healing and infection. In: Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, editors. Clinical Anaesthesia. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2009. p. 271-89.
5. Prys-Roberts C, Greene LT, Meloche R, Foëx P. Studies of anaesthesia in relation to hypertension. II. Haemodynamic consequences of induction and endotracheal intubation. Br J Anaesth 1971;43:531-47.
6. Kayhan Z, Aldemir D, Mutlu H, Ogüs E. Which is responsible for the haemodynamic response due to laryngoscopy and endotracheal intubation? Catecholamines, vasopressin or angiotensin? Eur J Anaesthesiol 2005;22:780-5.
7. Chung F, Evans D. Low-dose fentanyl: Haemodynamic response during induction and intubation in geriatric patients. Can Anaesth Soc J 1985;32:622-8.
8. Lowenstein E. Perianesthetic ischemic episodes cause myocardial infarction in human – a hypothesis confirmed. Anesthesiology 1985;62:103-6.
9. Ebret TJ, Schmid PG. Inhaled anaesthetics. In: Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, editors. Clinical Anaesthesia. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2009. p. 413-43.
10. Rantanen M, Yli-Hankala A, van Gils M, Yppärilä-Wolters H, Takala P, Huiku M, et al. Novel multiparameter approach for measurement of nociception at skin incision during general anaesthesia. Br J Anaesth 2006;96:367-76.
11. Kehlet H, Dahl JB. The value of “multimodal” or “balanced analgesia” in postoperative pain treatment. Anesth Analg 1993;77:1048-56.
12. White PF, Kehlet H, Neal JM, Schricker T, Carr DB, Carli F. Fast-Track Surgery Study Group. The role of the anaesthesiologist in fast-track surgery: From multimodal analgesia to perioperative medical care. Anesth Analg 2007;104:1380-96.
13. Macres SM, Moore PG, Fishman SM. Acute pain management. In: Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, editors. Clinical Anaesthesia. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2009. p. 147-504.
14. Duellman TJ, Gaffigan C, Milbrandt JC, Allan G. Multi-modal, pre-emptive analgesia decreases the length of hospital stay following total joint arthroplasty. Surg Technol Int 2009;32:167.
15. Nakata Y, Goto T, Saito H, Ishiguro Y, Terui K, Kawakami H, et al. Plasma concentration of fentanyl with xenon to block somatic and hemodynamic responses to surgical incision. Anesthesiology 2000;92:1043-8.
16. Channaiah V, Chary K, Vlk JL, Wang Y, Chandra BC. Low-dose fentanyl: Hemodynamic response to endotracheal intubation in normotensive patients. Arch Med Sci 2008;4:293-9.
17. Arora S, Kulkarni A, Bhargava AK. Attenuation of hemodynamic response to laryngoscopy and orotracheal intubation using intravenous clonidine. J Anaesthesiol Clin Pharmacol 2015;31:110-4.
18. Rosow CE, Levine WC. Drug interactions. In: Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, editors. Clinical Anaesthesia. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2009. p. 549-66.
19. Wadsworth R, Anderton JM, Vohra A. The effect of four different surgical prone positions on cardiovascular parameters in healthy volunteers. Anaesthesia 1996;51:819-22.
20. Backofen JE, Schauble JF. Hemodynamic changes with prone position during general anaesthesia. Anesth Analg 1985;64:194.
21. Yokoya M, Ueda W, Hirakawa M, Yamamoto H. Hemodynamic effect of the prone position during anesthesia. Acta Anaesthesiol Scand 1991;35:741-4.
22. Channabasappa SM, Shankarnarayana P. A comparative study of hemodynamic changes between prone and supine emergence from anesthesia in lumbar disc surgery. Anesth Essays Res 2013;7:173-7.
23. Katoh T, Kobayashi S, Suzuki A, Iwamoto T, Biyo H, Ikeda K. The effect of fentanyl on sevoflurane requirements for somatic and sympathetic responses to surgical incision. Anesthesiology 1999;90:398-405.
24. Johansen JW, Flaxhorn R, Sebel PS. Esmolol reduces anesthetic requirement for skin incision during propofol/nitrous oxide/morphine anesthesia. Anesthesiology 1997;86:364-71.