

Effect of tramadol on extubation response and quality of emergence following Supratentorial surgery: A randomised controlled trial

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Abstract

Objective: To observe the effect of a single dose of tramadol 1mg/kg on haemodynamic changes related to extubation, and to assess the quality of emergence as judged by incidence of cough, laryngospasm and bronchospasm.

Method: The double-blind randomised controlled trial was conducted at the Department of Anaesthesiology, Aga Khan University Hospital, Karachi, from 2016 to 2017, and comprised patients of either gender aged 18-65 years scheduled for elective supratentorial craniotomy under general anaesthesia. The patients were randomised to two Tramadol and Saline groups. The drug was given 45 minutes before extubation at the time of dura closure. The patients were extubated after resumption of adequate spontaneous breathing. Invasive blood pressure and heart rate were recorded one minute before reversal, at 1 minute interval for five minutes and then every 10 minute for 30 minutes after extubation. Cough, laryngospasm and bronchospasm were noted. Pain, post-operative nausea, vomiting, convulsions and conscious levels were also noted till 6 hours post-operatively. Data was analysed using SPSS 19.

Results: Of the 80 patients enrolled, 79(98.75%) completed the study. Of them, 38(48%) were in the Tramadol group; 27(71.1%) males and 11(28.9%) females with a mean age of 43.42 ± 13.2 years. The remaining 41(52%) patients were in the Saline group; 28(68.3%) males and 13(31.7%) females with a mean age of 45.9 ± 15.9 years. Intergroup comparison showed no significant difference in the extubation response ($p > 0.05$), but the changes in blood pressure and heart rate were shorter in magnitude and duration in the Tramadol group compared to the baseline. Significant rise in blood pressure and heart rate were observed in the Saline group at 5 minutes after extubation ($p = 0.046$). There was no difference in the quality of emergence as judged by cough or secondary complications ($p > 0.05$).

Conclusion: Tramadol 1mg/kg was considered superior in attenuating the duration and magnitude of haemodynamic response in the shape of hypertension and tachycardia during extubation, but did not affect other parameters in patients undergoing craniotomy.

Clinical Trial Number: Clinical Trials.gov PRS: NCT02964416
<https://clinicaltrials.gov/ct2/show/NCT02964416>

Keywords: Craniotomy, Endotracheal extubation, Haemodynamics, Opioid, Cough. (JPMA 72: 2160; 2022)

DOI: <https://doi.org/10.47391/JPMA.4082>

Introduction

Intracranial surgery requires smooth extubation with minimal haemodynamic variation, cough suppression and early awakening, in order to avoid complications, and to allow early assessment of patient's neurological status. Poorly controlled pain and coughing at extubation may lead to agitation, increased oxygen consumption, catecholamine secretion, systemic hypertension (HTN), and tachycardia^{1,2} which causes intracranial HTN, post-operative cerebral oedema and intracranial haemorrhage^{3,4} complicating the course after a successful craniotomy.⁵

Several medications and techniques have been investigated to obtund the haemodynamic response and suppress cough during emergence, including extubation

in a deep plane of anaesthesia, and use of short-acting opioids or morphine prior to extubation. Short-acting opioids have been investigated during emergence⁴ and have shown equivocal results.^{6,7} To date, no standard of care is recommended.⁸ Availability of short-acting narcotics is also an issue in many low-income countries (LICs), including Pakistan.^{9,10} Tramadol, however, is readily available and is widely used for peri-operative analgesia. Addition of tramadol to the anaesthesia regimen has led to better pain relief and reduction in cough intensity at extubation.^{11,12} However, limited literature is available for its use in suppressing the haemodynamic response to tracheal extubation, especially in neuroanaesthesia.

The current study was planned to observe the effect of a single dose of tramadol on haemodynamic changes, and to determine its effects on incidence of cough, bronchospasm, laryngospasm or desaturation at extubation, as well as post-operative outcomes, like post-operative nausea vomiting (PONV), convulsions, level of

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consciousness and the requirement of analgesia.

Patients and Methods

The double-blind randomised controlled trial (RCT) was conducted at the Department of Anaesthesiology, Aga Khan University Hospital (AKUH), Karachi, over a period of two years from 2016 to 2017. The RCT was registered with the Protocol Registration and Results System, Clinical Trials.gov PRS (NCT02964416). After approval from the institutional ethics review committee, the sample size was estimated based on a previous study⁵ while keeping 80% power to detect an absolute difference of 10mmHg and standard deviation of 10-15 mmHg with type I error 5% in the systolic blood pressure (SBP). The sample was inflated to account for a 15% dropout rate.

Those included were patients of either gender aged 18-65 years scheduled for elective supratentorial craniotomy under general anaesthesia, American Society of Anesthesiologists (ASA) status 2 or 3 and with a Glasgow Coma Scale (GCS) score 15/15. Obese patients, those with raised intracranial pressure (ICP), patients with history of convulsions or epilepsy, and patients with language barrier were excluded, and so were those taking monoamine oxidase inhibitors, beta (β) blockers or calcium channel blockers, and those with chronic usage of analgesic drugs.

Patients were recruited in the study during the pre-operative anaesthesia evaluation either at the pre-operative clinic or after admission to the ward. After taking informed written consent, the patients randomised into intervention group A and placebo group B. Each medical record number was sent to the Clinical Trials Unit (CTU) along with their expected date, day and timing of surgery. The CTU randomly allocated the patients to one of the two groups based on computer-generated allocation. After the patient reached the pre-operative area in the operating room (OR), an e-mail request was generated to the CTU, and a prepared study drug syringe was received by the principal investigator (PI). The syringe contained either tramadol 10mg/ml in a 10 ml syringe or placebo 0.9% normal saline in the same volume. Drugs for both the groups looked alike, and the patient, the investigator, the anaesthetist administering the drugs or those making observations were all blinded. Later, data analysers were also kept blinded, making the study triple blind. Intra-operatively, anaesthesia care was standardised.

After the application of electrocardiography (ECG), non-invasive blood pressure (NIBP) monitor and pulse oximeter, baseline heart rate (HR), blood pressure (BP) and oxygen saturation (SpO_2) were recorded. Pre-oxygenation was done for 3 minutes with oxygen administered at a rate of 5 l/min via a breathing circuit. Anaesthesia induction was

done with propofol (2 mg/kg) intravenously (IV) and fentanyl (2 μ g/kg) IV, followed by atracurium (0.6mg/kg) IV. Maintenance of anaesthesia was achieved with oxygen (O_2), nitrous oxide (N_2O) in 1:2 ratio, isoflurane (0.8-1%) and atracurium infusion (0.4 mg/kg/hr). Ventilation was set at 8 ml/kg, volume controlled mode and respiratory rate was adjusted to achieve a level of end-tidal carbon dioxide ($ETCO_2$) of 29-30 mmHg. An arterial line was inserted in radial artery for continuous invasive BP monitoring. ECG, SpO_2 , capnography, inspiratory and expiratory concentrations of isoflurane minimum alveolar concentration (MAC) and N_2O percentage, as well as neuromuscular block, were continuously monitored. Paracetamol 1gm was infused over 20 min in all patients after induction. Top-up fentanyl 20 μ g boluses were administered if either the patient's HR or BP increased to 20% above the baseline and when other causes of tachycardia and HTN were excluded. Atracurium infusion was stopped 20 min before the end of the surgery. Injection metoclopramide 10 mg was given to all patients at the time of closure of dura.

The study drug (tramadol 1 mg/kg or normal saline bolus) was administered to the patients by the anaesthetist 45min before extubation, i.e. approximately at the time of dural closure. Reversal of residual muscle relaxation was achieved with neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg) IV, and time was noted when the patient started breathing spontaneously. Patients were extubated after resumption of adequate spontaneous breathing, following verbal commands and with stable vital signs.

BP and HR were recorded continuously from the arterial line, at 1min before the administration of reversal drugs till 5min after extubation, then intermittently at 10min interval for 30 min. Readings at 1, 2, 4 and 6 hours were recorded post-operatively using non-invasive methods (CARESCAPE Monitor B650, GE Healthcare Ltd, Finland). IV metoprolol 1mg bolus was administered when haemodynamic values of BP and HR rose >20% from the baseline values.

Cough was recorded as either "yes" or "no" at the resumption of spontaneous breathing, when patients were able to respond to verbal commands, at the time of cuff deflation, at extubation and 2 min post-extubation. Quality of tracheal extubation was evaluated using a modified 5-point rating scale at the above-mentioned intervals, (5 = no coughing or straining; 4 = very smooth or minimal coughing; 3=moderate coughing; 2 = marked coughing or straining; and 1=poor extubation).⁵ Any episode of bronchospasm, laryngospasm or desaturation (oxygen saturation <92%) was noted during emergence and till 6 hours post-operatively. Sedation, PONV, any episode of convulsions and drop in GCS were also noted at 2, 4 and 6h

post-operatively as secondary outcomes of quality of emergence. The study ended at 6 hours post-extubation.

Pain was assessed for 6h post-operatively using verbal rating scale (VRS) with 0=no pain and 10=worst pain. Sedation was assessed as 0=no sedation, 1=mild sedation (eye-opening on verbal commands), 2=moderate sedation (eye-opening on painful stimulus), 3=deep sedation (not waking up on pain). All patients were prescribed paracetamol 1 gm IV six hourly and tramadol 50 mg IV as rescue analgesia in the first 6 hours post-operatively. Anti-emetic prophylaxis was given with each dose of tramadol.

Data was analysed using SPSS 19. Quantitative point estimate was presented as mean and standard deviation, and analysed using independent sample t-test and Mann-Whitney U test after normality testing by Kolmogorov Smirnov test. Qualitative point estimates were reported as frequencies and percentages, and were analysed using chi-square test or fisher exact test. Repeated measure analysis of variance (ANOVA) was applied to compare mean SBP, DBP and HR values between the groups, and were reported with 95% confidence interval (CI). $P \leq 0.05$ was considered statistically significant.

Results

Of the 80 patients enrolled, 79(98.75%) completed the study (Figure-1). Of them, 38(48%) were in the tramadol group A; 27(71.1%) males and 11(28.9%) females with a mean age of 43.42 ± 13.2 years. The remaining 41(52%) patients were in the placebo group B; 28(68.3%) males and 13(31.7%) females with a mean age of 45.9 ± 15.9 years (Table 1). Intergroup comparison showed no significant difference in the extubation response ($p > 0.05$), but the changes in BP and HR were

Table-1: Comparison of demographics and characteristics between the groups.

Variables	Tramadol n (%) (n=38)	Placebo n (%) (n=41)
Mean Age (year)	43.42±13.2	45.9±15.9
Mean Height (cm)	164.78±10.2	162.43±8.12
Mean Weight (kg)	71.4±16.1	71.3±12.8
Mean Body mass index (BMI) (kg/m ²)	26.2±4.80	27.1±4.88
Gender		
Male	27 (71.1)	28 (68.3)
Female	11 (28.9)	13 (31.7)
Comorbidity		
Hypertension	16 (42.1)	16 (39.0)
Diabetes Mellitus	9 (23.7)	8 (19.5)
Ischaemic heart disease	1 (2.60)	2 (4.90)
Asthma	1 (2.60)	1 (2.40)
Others	5 (13.2)	3 (7.20)

Values are presented as mean (SD) for age height, weight and BMI and in number (%) for gender and comorbidities.

Table-2: Comparison of coughing at emergence between the groups.

Time of occurrence of coughing	Tramadol n (%) (n=38)	Placebo n (%) (n=41)	Difference [95%CI] (%)	p-value
Resumption of regular spontaneous breathing	5(13.2)	5(12.2)	1[-13.7 to 15.7]	0.99
Obeying of verbal commands	4(10.5)	4(9.80)	0.7[-12.6 to 14]	0.99
Cuff deflation	4(10.5)	8(19.5)	-9[-24.6 to 6.6]	0.266
Extubation	6(15.8)	9(22)	-6.2[-23.4 to 11]	0.485
Two minutes after extubation	2(5.30)	4(9.80)	-4.5[-16.1 to 7.1]	0.451

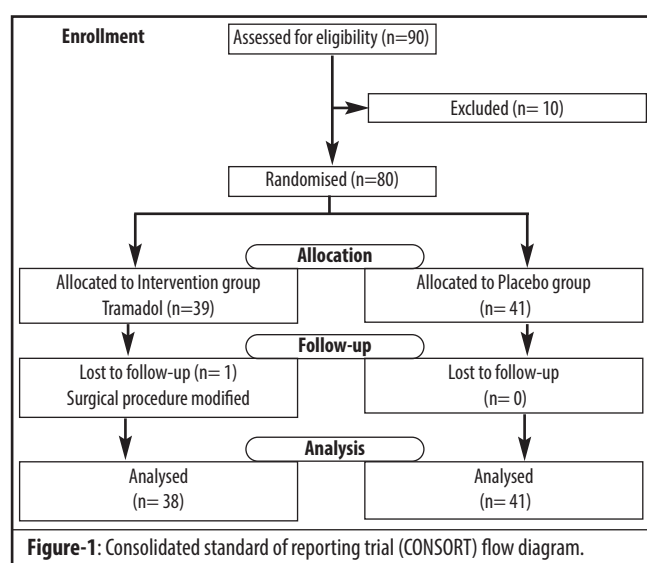
Values are presented as n (%). CI: Confidence interval.

shorter in magnitude and duration in the group A compared to the baseline (Figure 2).

Significant rise in BP and HR was observed in group B at 5min post-extubation ($p=0.046$). There was no difference in the quality of emergence as judged by cough or secondary complications ($p > 0.05$) (Table 2).

No significant difference was observed in the timing of administration of the last dose of narcotic and extubation between the groups ($p > 0.05$). The time duration from injection to extubation was 45-60 min in all cases.

None of the patients in either group had bronchospasm, laryngospasm or breath-holding during the observation period. Overall, 34(43%) patients had a temporary period of desaturation lasting a few seconds; 19(46.3%) in group B compared to 15(39.5%) in group A at the time of resumption of breathing and cuff deflation ($p=0.379$). In 1(2.6%) patient in group A convulsions were noted in the immediate post-extubation period and the GCS dropped to 10/15. The seizure activity was controlled using antiepileptic medication following which the GCS improved to 13/15 within 2 hours and was 15/15 within 4 hours.



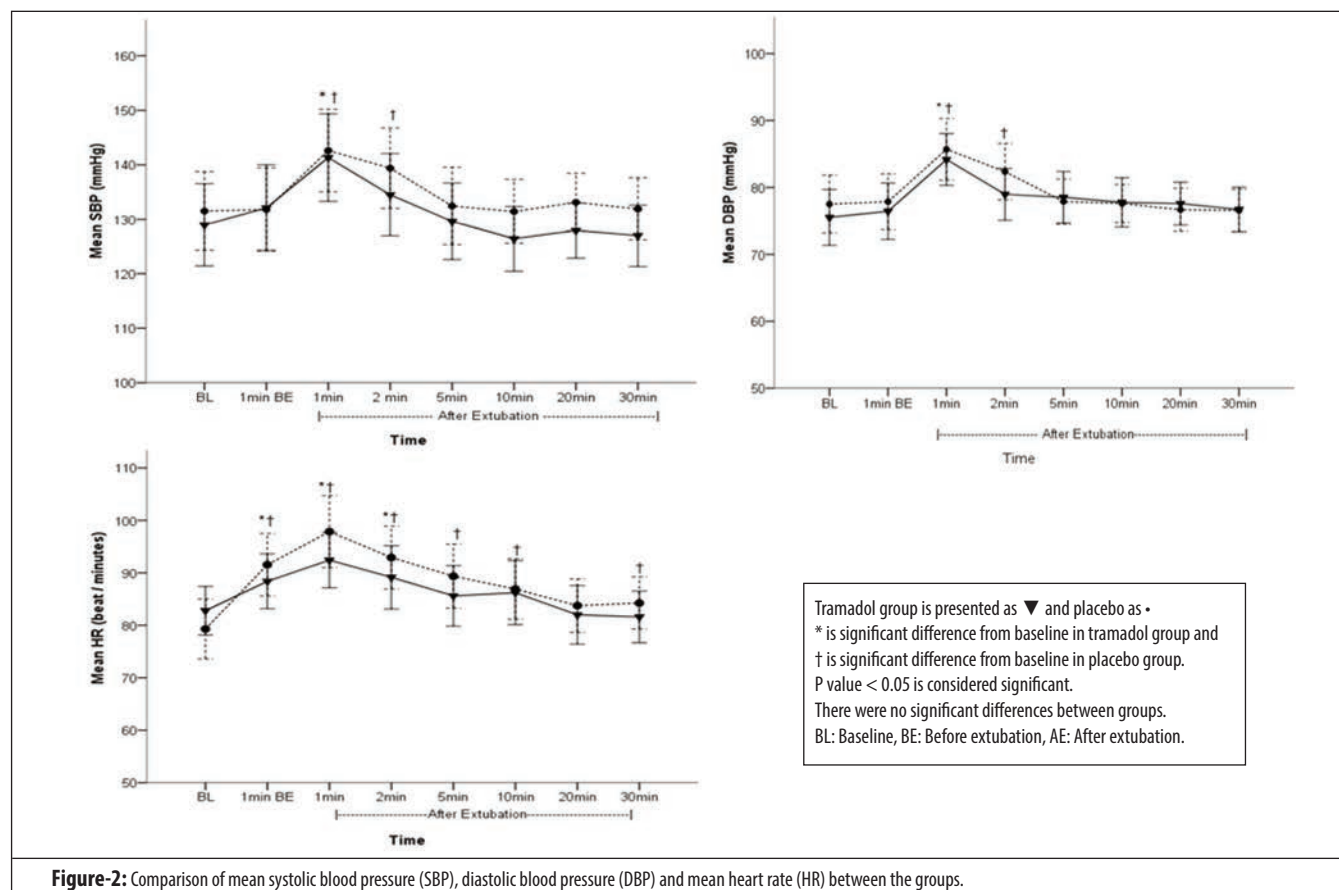


Figure-2: Comparison of mean systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean heart rate (HR) between the groups.

Overall, 23(60.5%) patients in group A and 29(70.7%) in group B required additional post-operative analgesia ($p=0.339$).

Discussion

Tramadol has mostly been used for post-operative pain management in surgical specialties, like obstetric, cardiothoracic and orthopaedics.⁶ There is limited literature on the use of tramadol at the time of tracheal extubation. Ikbal et al. studied the effects of tramadol in children and showed that its effect on quality of emergence compared to other drug was inconclusive as the time to extubate and eye-opening was shorter in the tramadol group compared to the other drug.¹² Likewise, Bedirili et al. also showed the superiority of tramadol on parameters at emergence, but in paediatric patients.¹³ Only one study investigated the use of tramadol during emergence, including its effect on haemodynamic response, restlessness, cough, and laryngospasm in adults, but the type of surgeries were not mentioned.¹⁴

In neurosurgery, the use of tramadol as analgesic at extubation is very limited. Few have investigated the use of tramadol for post-operative analgesia in neurosurgery,^{9,15,16} and there is limited literature on its use

for attenuation of haemodynamic response at extubation and quality of extubation in patients undergoing craniotomy. The scarcity in literature is attributed to the use of short-acting narcotics, like fentanyl, in craniotomy patients.

Lin et al. looked at the quality of emergence in patients undergoing laminectomy procedures and compared fentanyl and tramadol. Mean HR and BP at emergence was lower in the tramadol group than the fentanyl group. Patients had less incidence of cough in the tramadol group.⁵ The current study showed similar results.

The current study found no difference in coughing at extubation, need of analgesia, sedation, PONV and in other secondary complications. Talikoti et al. had also observed a lower incidence of cough between saline and tramadol groups, but they did not mention the statistical significance of the findings.¹⁴ The incidence of cough with tramadol in the current study was similar to their findings. A temporary drop in oxygen saturation <92% was observed in 19% patients in the placebo group and 15% in the tramadol group, but this was not statistically different. In none of the patients, fall in SpO₂ needed intervention. This drop probably indicated transient upper airway obstruction.

The current study rarely found any serious or prolonged complications in either of the two groups. These findings are comparable with the study done by Lu et al. who implemented the Enhanced Recovery after Surgery (ERAS) protocol in elective craniotomy patients and used tramadol as additional analgesic in both groups. Post-operative complications were comparable between the groups.¹⁷ The current study used anti-emetic prophylactically in all patients and continued it along with narcotic injection till 24h in the post-operative period. Probably this was the reason for overall less PONV.

In 1 patient in the tramadol group, BP needed to be controlled with glyceryl trinitrate (GTN) 100 µg at 2 min post-extubation. In the placebo group, 2 patients required treatment for HTN based on haemodynamic parameters. The first patient needed two boluses of IV metoprolol (1 mg each) and remained fine afterwards, while the second patient received metoprolol 1mg and glyceryl trinitrate (GTN) 200 µg over 5min. This patient had a GCS 13/15 at extubation. After 2h GCS dropped to 10 and required re-intubation in the recovery room. He was shifted to the critical care unit. The reason found was diabetes insipidus (DI) in this patient, which resolved after treatment with desmopressin. One patient in the tramadol group also had a low GCS of 10 post-extubation for 2h, but the GCS improved within 4 hours to 13 and the patient was fully conscious by 6 hours. The reason for low GCS in this later patient was probably surgical manipulation.

The current study has a few limitations. Firstly, it was unable to analyse sedation scores due to missing information on the forms. Secondly, the study was not powered to observe the statistical difference between secondary complications. Also, several confounding factors, like pain, ETCO₂ levels, residual inhalational agent concentration, patients temperature, and fluid status, can affect the haemodynamic response to extubation. We tried to standardise these as much as possible in methodology, but there is a possibility that some of these could result in variation in hemodynamic response at the time of extubation. Lastly, although the mean elimination half-life of tramadol is 5-6 hours,¹⁸ in some patients the effects may last beyond 6h, but the study was terminated at 6 hours.

Conclusion

A single 1 mg/kg dose of tramadol IV administered approximately 45 min before extubation can obtund and shorten the haemodynamic response to tracheal extubation compared to the baseline in patients undergoing supratentorial craniotomy. There was no advantage in reduction of cough in the tramadol group compared to the placebo group. Side effects, like PONV and

sedation, were not significantly different between the groups.

Disclaimer: None.

Conflict of interest: None.

Source of Funding: None.

References

1. Halder R, Kaushal A, Gupta D, Srivastava S, Singh PK. Pain following craniotomy: reassessment of the available options. *Biomed Res Int* 2015;2015:e509164. doi: 10.1155/2015/509164.
2. Chowdhury T, Garg R, Sheshadri V, Venkatraghavan L, Bergese SD, Cappellani RB et al. Perioperative Factors Contributing the Post-Craniotomy Pain: A Synthesis of Concepts. *Front Med (Lausanne)* 2017;4:e23. doi: 10.3389/fmed.2017.00023.
3. Attari M, Tayyari F, Narimani N. Comparing the Effect of Labetalol versus Morphine on Controlling Blood Pressure and Pulse Rate during Emergence from Anesthesia after Craniotomy. *Adv Biomed Res* 2017;6:e127. doi: 10.4103/2277-9175.216781.
4. Ayrian E, Kaye AD, Varner CL, Guerra C, Vadivelu N, Urman RD, et al. Effects of Anesthetic Management on Early Postoperative Recovery, Hemodynamics and Pain After Supratentorial Craniotomy. *J Clin Med Res* 2015;7:731-41. doi: 10.14740/jocmr2256w.
5. Lin BF, Ju DT, Cherng CH, Hung NK, Yeh CC, Chan SM, et al. Comparison between intraoperative fentanyl and tramadol to improve quality of emergence. *J Neurosurg Anesthesiol* 2012;24:127-32. doi: 10.1097/ANA.0b013e31823c4a24.
6. Choi EK, Kwon N, Park SJ. Comparison of the effects of oxycodone versus fentanyl on airway reflex to tracheal extubation and postoperative pain during anesthesia recovery after laparoscopic cholecystectomy: A double-blind, randomized clinical consort study. *Medicine (Baltimore)* 2018;97:e0156. doi: 10.1097/MD.00000000000010156.
7. Dutta D, Godara M, Purohit S, Kalra P, Sharma SP, Gill N. Comparison of the effect of intravenous dexmedetomidine and lignocaine spray instilled into the endotracheal tube on extubation response in patients undergoing spine surgery. *J Neuroanaesthesiol Crit Care* 2016;3:239-44. doi: 10.4103/2348-0548.190070
8. Ayrian E, Kaye AD, Varner CL, Guerra C, Vadivelu N, Urman RD, et al. Effects of Anesthetic Management on Early Postoperative Recovery, Hemodynamics and Pain After Supratentorial Craniotomy. *J Clin Med Res* 2015;7:731-41. doi: 10.14740/jocmr2256w.
9. Cooper TE, Fisher E, Gray AL, Krane E, Sethna N, van Tilburg MA, et al. Opioids for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev* 2017;7:CD012538. doi: 10.1002/14651858.CD012538.pub2.
10. Pastrana T, Wenk R, Radbruch L, Ahmed E, De Lima L. Pain Treatment Continues To Be Inaccessible for Many Patients Around the Globe: Second Phase of Opioid Price Watch, a Cross-Sectional Study To Monitor the Prices of Opioids. *J Palliat Med* 2017;20:378-87. doi: 10.1089/jpm.2016.0414.
11. Wong TH, Weber G, Abramowicz AE. Smooth Extubation and Smooth Emergence Techniques: A Narrative Review. *Anesthesiol Res Pract* 2021;2021:e8883257. doi: 10.1155/2021/8883257.
12. Koceroglu I, Devrim S, Bingol Tanriverdi T, Gura Celik M. The effects of dexmedetomidine and tramadol on post-operative pain and agitation, and extubation quality in paediatric patients undergoing adenotonsillectomy surgery: A randomized trial. *J Clin Pharm Ther* 2020;45:340-6. doi: 10.1111/jcpt.13080.
13. Bedirli N, Akçabay M, Emik U. Tramadol vs dexmedetomidine for emergence agitation control in pediatric patients undergoing adenotonsillectomy with sevoflurane anesthesia: prospective

- randomized controlled clinical study. *BMC Anesthesiol* 2017;17:41. doi: 10.1186/s12871-017-0332-4.
14. Talikoti DG, Karigar SL, Mulimani S. Tramadol attenuates the post anaesthetic emergence events-a randomized clinical trial. *Indian J Clin Anaesth* 2016;3:455-8. doi: 10.5958/2394-4994.2016.00077.9
 15. Hassani E, Mahoori A, Sane S, Tolumehr A. Comparison the effects of paracetamol with sufentanil infusion on postoperative pain control after craniotomy in patients with brain tumor. *Adv Biomed Res* 2015;4:e64. doi: 10.4103/2277-9175.152610.
 16. Dogar SA, Khan FA. Tramadol-Paracetamol Combination for Postoperative Pain Relief in Elective Single-level Microdisectomy Surgery. *J Neurosurg Anesthesiol* 2017;29:157-60. doi: 10.1097/ANA.0000000000000274.
 17. Qu L, Liu B, Zhang H, Sankey EW, Chai W, Wang B, et al. Management of Postoperative Pain after Elective Craniotomy: A Prospective Randomized Controlled Trial of a Neurosurgical Enhanced Recovery after Surgery (ERAS) Program. *Int J Med Sci* 2020;17:e1541-9. doi: 10.7150/ijms.46403.
 18. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in Tramadol: Pharmacology, Metabolism, and Misuse. *Anesth Analg* 2017;124:44-51. doi: 10.1213/ANE.0000000000001683.
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