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Efficacy of Ketamine as an Adjuvant to Scalp Block for Hemodynamic Stability in Patients Undergoing Elective Craniotomy for Supratentorial Glioma: A Prospective Randomized Controlled Trial

Ashutosh Kaushal[1] Sharmishtha Pathak[2] Priyanka Gupta[3] Praveen Talwar[3] Anuj Jain[1] Sunaina Tejpal Karna[1]

[1] Department of Anaesthesiology, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India
[2] Department of Anaesthesiology, Pain Medicine and Critical Care, Jai Prakash Narayan Apex Trauma Center, All India Institute of Medical Sciences, Delhi, India
[3] Department of Anaesthesiology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

Address for correspondence Sharmishtha Pathak, DM, MD, Department of Anaesthesiology, Pain Medicine and Critical Care, Jai Prakash Narayan Apex Trauma Center, All India Institute of Medical Sciences, New Delhi 110029, India (e-mail: sharmishtha.pathak@gmail.com).

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Abstract

Introduction Scalp nerve block (SNB) attenuates the hemodynamic response to pin insertion and delivers excellent postoperative analgesia. This study aimed to evaluate the efficacy of SNB using ketamine as an adjuvant to bupivacaine on perioperative hemodynamic responses and postoperative pain in patients undergoing craniotomy for supratentorial glioma.

Materials and Methods Sixty patients were randomized into two groups. They were given scalp nerve block either with bupivacaine and saline (group S) or bupivacaine and ketamine (group K). Primary outcome was to compare the change in mean arterial pressure (MAP) and heart rate (HR) at defined time points from baseline. Secondary outcomes included time to request for first analgesia, total analgesic consumption in intraoperative and postoperative periods till 24 hours, and numeric rating scale pain score at various time points in postoperative period till 24 hours.

Results Fifty-seven patients were included in analysis. HR and MAP were comparable intraoperatively till closure. As soon as closure began, a significant increase in HR (group K vs. group S, 69.76 ± 9.03 vs. 93.96 ± 9.98, p-value $= < 0.0001$) and MAP (group K vs. group S, 79.4 ± 4.12 vs. 87.17 ± 12.67, p-value $= 0.002$) was noted in group S patients. This increase persisted in the postoperative period as well. The median total opioid consumed during intraoperative period in group K was 200 mcg versus 300 mcg in group S, p-value < 0.0001.

Conclusion Adding ketamine as an adjuvant to bupivacaine for SNB not only provides significant hemodynamic stability but also reduces both intra- and postoperative analgesic consumption.

Keywords
- ketamine
- numeric rating scale (NRS)
- opioid
- rescue analgesia
- scalp nerve block

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Introduction

Strong noxious stimulus and sympathetic activation due to head fixation by skull pin head clamp during craniotomy produce a sudden rise in heart rate (HR) and blood pressure, which might lead to increased cerebral blood flow and intracranial pressure (ICP).[1–3] In addition, nearly 30% of the patients experienced moderate pain, whereas 10 to 20% of the patients suffered from severe pain in the postoperative period after craniotomy.[4] Scalp nerve block (SNB) with local anesthetics (LA) proved to be an efficient means of controlling the hemodynamic response to pin insertion and delivering excellent and safe postoperative analgesia.[5–8] Previous studies have shown a beneficial effect of adding clonidine, dexmedetomidine, dexamethasone, and epinephrine to LA for SNB in attenuating hemodynamic response to skull pin insertion as well as prolonging the effect of SNB.[2,3,9]

Ketamine is an intravenous induction agent with LA activity and thus affects nerve conduction significantly. It is an N-methyl-D-aspartate (NMDA) receptor antagonist with reported central, regional, and LA and analgesic properties. Conventionally, ketamine has not been used for neurosurgical patients because it is a potent cerebral vasodilator, which may increase ICP.[10] However, several studies have found that when ketamine is administered along with other neuroanaesthetic agents, ICP remains stable.[11–13]

The addition of ketamine to bupivacaine in epidural/regional nerve blocks (brachial plexus blocks) has been shown to increase the duration of regional anesthesia and postoperative analgesia.[14]

However, SNB with LA infiltration alone and along with ketamine has not been compared yet. We hypothesized that adding ketamine, a NMDA receptor antagonist, to bupivacaine not only provides a better hemodynamic profile than bupivacaine alone during skull pin application but will also prolong the postoperative analgesia.

This study aimed to evaluate the efficacy of SNB using ketamine as an adjuvant to bupivacaine on perioperative hemodynamic responses and postoperative pain in patients undergoing craniotomy for supratentorial glioma under general anesthesia.

Materials and Methods

This prospective randomized control study was conducted at a tertiary care center from December 2019 to June 2021 after obtaining approval from the Institutional Ethics Committee (AIIMS/IEC/19/1101). The trial was registered under the Clinical Trial Registry, India (CTRI/2019/11/022165).

Patients aged 18 to 65 years, of either gender, belonging to the American Society of Anesthesiologists (ASA) physical status I and II undergoing elective craniotomy for supratentorial glioma were enrolled after getting written informed consent. Patients who refused consent, had proven or suspected allergy to study drugs, Glasgow Coma Scale (GCS) < 15, history of psychotic disorders or previous surgery, poor cognitive function, those intended for elective ventilation overnight, those suffering from chronic headache or on analgesics for a long duration, uncontrolled hypertension, diabetes mellitus, or heart disease were all excluded from the study. The patients who required reintubation during the study period or those who were not extubated immediately after surgery due to any reason, and those who woke up with a deficit impairing their judgment of pain were also excluded from the final analysis.

All eligible patients were properly explained about the numerical pain rating scale (numeric rating scale [NRS]) (0–10, with 0 = no pain, 10 = worst pain ever) before surgery.[15]

The G*power 3.1 software was used to estimate the study sample size. With two-tail hypotheses, assuming α (type I error) of 5% and power of 95%, presuming a 10% difference in HR to be significant in the two groups, 30 patients in each group were calculated.

Sixty patients were randomly allocated to one of the two groups (K and S) based on a sequence of computer-generated random numbers with an allocation ratio of 1:1. The sealed opaque envelope method was used for allocation concealment. The sealed envelope was opened by the anesthesiologist who was not part of the study to determine the group of the patient. The same anesthesiologist prepared the respective drug (15 mL) in a syringe and labeled it as a study drug. The patient and the anesthesiologist performing the block were blinded to the patient's allocation.

Once the patient was wheeled into the operating room, standard monitoring was employed, including electrocardiography, noninvasive blood pressure, pulse oximetry (SpO2), and axillary temperature. After preoxygenation with 100% O2 at 6 L/min, anesthesia was induced using the standard institutional protocol (injection fentanyl 2 mcg/kg, propofol 2 mg/kg, and rocuronium 1 mg/kg), and the airway was secured with a tracheal tube of appropriate size. Anesthesia was maintained with sevoflurane in O2:N2O (40:60) to achieve 0.5 to 1 minimum alveolar concentration in both groups.

Bilateral scalp blocks were performed after induction of anesthesia using a 25-G needle to infiltrate respective drugs to supraorbital, supratrochlear, zygomaticotemporal, auriculotemporal, lesser occipital, and greater occipital nerves in both groups. Group S patients (control group) were given scalp block using 12 mL 0.5% bupivacaine with 3 mL saline, while group K patients received scalp block using 12 mL 0.5% bupivacaine with 3 mL (2 mg/kg) ketamine. Intravenous fentanyl (2 mcg/kg/h) and rocuronium(0.2 mg/kg/h) were given as infusions to maintain hemodynamic stability. End-tidal carbon dioxide was maintained between 30 and 35 mm Hg. Intraoperatively, the nasopharyngeal temperature was measured, and euthermia was maintained. Once the dura was opened, the surgeon was asked to comment upon the brain relaxation and graded as 1–perfectly relaxed, 2–satisfactorily relaxed, 3–firm brain, and 4–bulging brain.[16]

Systolic arterial pressure, diastolic arterial pressure, mean arterial pressure (MAP), and HR were recorded at baseline, 1 minute, and 5 minutes after induction of anesthesia, during head pinning, at skin incision, 60 minutes after skin incision, during skin closure, and just after extubation. After completion of the surgery, anesthesia was reversed, and the trachea

was extubated according to standard anesthesia protocol. Patients' severity of pain was assessed just after extubation, followed by 1, 2, 4, 8, 16, and 24 hours postextubation with the help of a NRS score.

Postoperatively, all the patients received 1 g paracetamol 8 hourly for postoperative analgesia, and if patients complained of pain (NRS score >4) injection tramadol 100 mg intravenously was administered as rescue analgesic. The time duration from extubation to the request for the first analgesia was noted. Postoperative analgesic consumption, as well as complications like hemodynamic instability (hypertension, tachycardia, bradycardia, hypotension), postoperative nausea vomiting, or any other postoperative complications, were also recorded.

Intraoperatively, bradycardia (HR $<20\%$ from baseline), tachycardia (HR $>20\%$ from baseline), hypertension (MAP $>20\%$ from baseline), and hypotension (MAP $<20\%$ from baseline) were recorded and treated. Intravenous atropine 0.6 mg was administered to treat bradycardia, whereas tachycardia was treated with an intravenous bolus dose of esmolol (100 µg/kg). Hypotension was treated with a bolus dose of injection mephentermine 6 mg intravenously, whereas hypertension was treated with intravenous propofol in increments of 10 mg.

The primary outcome of the study was to compare the change in mean arterial blood pressure and HR at defined time points from the baseline in both groups.

The secondary outcomes were to compare the time duration after extubation to request for the first analgesia, total analgesic consumption in the intraoperative and postoperative period till 24 hours, and NRS pain score at various time points in the postoperative period till 24 hours.

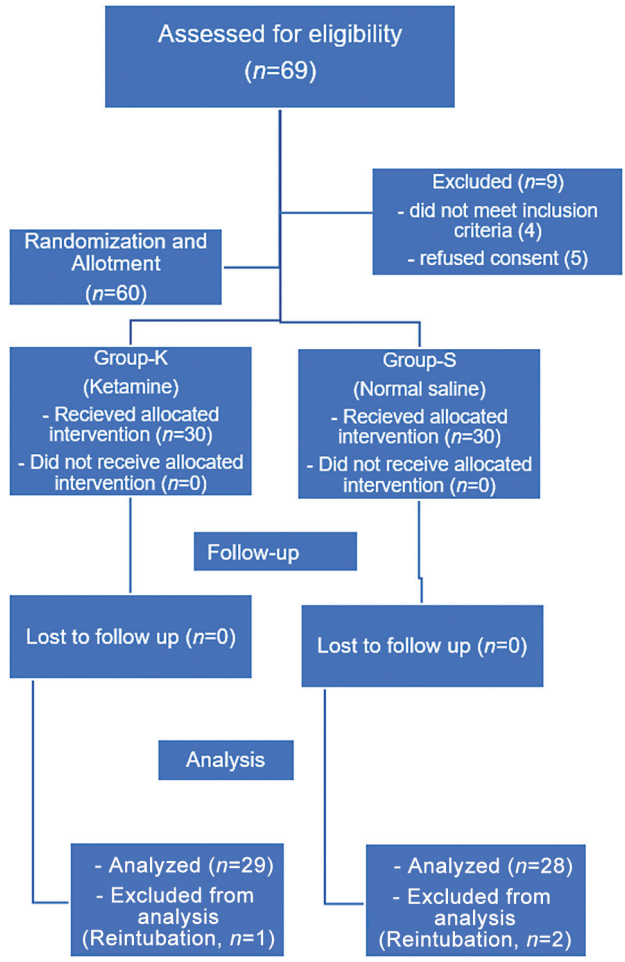

Fig. 1 CONSORT flow diagram.

Statistical Analysis

The data was entered in Microsoft EXCEL and analyzed using Statistical Package for Social Sciences software (IBM, Chicago, Illinois, United States, ver 21.0). The quantitative data with normal distribution were presented as the mean $\pm$ standard deviation and the data with nonnormal distribution as median with 25th and 75th percentiles (interquartile range [IQR]). The data normality was checked by using the Kolmogorov–Smirnov test. The cases in which the data was not normal, nonparametric tests were used. The comparison of the variables, which were quantitative and not normally distributed in nature, was analyzed using the Mann–Whitney test. An independent *t*-test was used for comparison between two groups of normally distributed data. Variables that were qualitative in nature were analyzed using the chi-square test. If any cell had an expected value of less than 5, then the Fisher's exact test was used. For statistical significance, a *p*-value of less than 0.05 was considered significant.

Results

A total of 69 patients were assessed for eligibility, and 60 patients were included and randomized. The Consort flowchart is shown in ►**Fig. 1**. Out of the 60 patients who received the allocated intervention, one from group K and 2 from group S were reintubated in the postoperative period due to deterioration in GCS and hence were excluded from the final analysis. Patients' demographic characteristics (age, gender), ASA physical status, total duration of surgery, and anesthesia were comparable in both groups (►**Table 1**).

The HRs were comparable among the two groups at baseline and for the entire duration of surgery, except at the time of skin closure. It was observed that during skin closure, the HR was significantly less in group K (69.76 ± 9.03) than in group S (93.96 ± 9.98), with a *p*-value <0.0001, as shown in ►**Table 2**. In the postoperative period as well the HR was found to be significantly less at all time intervals in group K in comparison to group S, with a *p*-value less than 0.05 at all times (►**Table 2**).

MAP at baseline was comparable between the two groups. The values remained comparable throughout the intraoperative period except at skin closure when MAP was 79.4 ± 4.12 in group K and 87.17 ± 12.67 in group S (*p*-value 0.002). This difference between the two groups continued in the postoperative period as well and was found to be statistically significant even 24 hours after extubation, with a *p*-value of 0.049 (►**Table 3**).

The median total opioid consumed during the intraoperative period in group K was 200 mcg, while that in group S was 300 mcg. The difference was statistically significant

Table 1 Sociodemographic and intraoperative characteristics between groups K and S

Sociodemographic characteristics	Group K ($n = 29$)	Group S ($n = 28$)	*p*-Value
Age (y), *n* (range)	49 (23–60)	42 (22–61)	0.992[a]
Gender			
Female, *n* (%)	12 (41.3)	12 (42.8)	1[b]
Male, *n* (%)	17 (58.6)	16 (57.1)	
ASA grade, *n* (%)			
I	12 (41.3)	16 (57.14)	0.531[c]
II	17 (58.6)	12 (42.8)	
Duration of surgery (min)	255 (170–360)	270 (150–420)	0.561[a]
Duration of anesthesia (min)	325 (225–420)	315 (195–470)	0.810[a]

Abbreviation: ASA, American Society of Anesthesiologists.
[a]Mann–Whitney test.
[b]Chi-square test.
[c]Fisher's exact test.

Table 2 Comparison of perioperative heart rate between groups K and S

Perioperative heart rate (beats/min)	Group K ($n = 30$)	Group S ($n = 30$)	*p*-Value
At baseline	87 ± 12.46	82.5 ± 13.65	0.185[a]
1 minute after induction	80.6 ± 12.01	79.93 ± 13.97	0.84[a]
5 minutes after induction	78.43 ± 11.56	76.23 ± 13.11	0.49[a]
During head pinning	75.5 ± 11.03	77 ± 10.65	0.59[a]
At skin incision	76.46 ± 9.66	76.9 ± 11.69	0.87[a]
60 minutes after incision	73.83 ± 7.55	76.73 ± 10.95	0.23[a]
During skin closure	69.76 ± 9.03	93.96 ± 9.98	< **0.0001**[a]
Extubation	71.2 ± 12.62	92.86 ± 10.82	< **0.0001**[a]
1 hour postextubation	73.4 ± 9.6	81.13 ± 6.98	**0.0007**[a]
2 hours postextubation	72.73 ± 7.56	80.56 ± 8.05	**0.0003**[a]
4 hours postextubation	70.8 ± 8.98	92.93 ± 10.77	< **0.0001**[a]
8 hours postextubation	72.36 ± 12.12	91.53 ± 12.39	< **0.0001**[a]
16 hours postextubation	72.86 ± 13.46	86.43 ± 9.33	< **0.0001**[a]
24 hours postextubation	72.93 ± 10.27	83.6 ± 8.13	< **0.0001**[a]

[a]Independent *t*-test.
Note: *p*-value of < 0.05 is considered significant.

with a *p*-value < 0.0001. The patients in group K had significantly lower pain scores at all times as compared to group S patients (►**Fig. 2**).

On comparison of analgesic consumption by the patients in the postoperative period, it was found that the addition of ketamine to the scalp block significantly reduced the postoperative consumption of analgesics. The median opioid consumption in group S was 300 mg (200–400), while in group K, it was 100 mg (0–200), the difference was statistically significant (*p*-value < 0.00001).

The first dose of rescue analgesia was administered immediately after extubation to 14 patients in group S, while only 1 patient asked for analgesic immediately following extubation in group K, *p*-value $= 0.0002$ (►**Fig. 3**). All the patients of group S had requested for rescue analgesic by 2 hours following extubation, while the average duration for request to rescue analgesic was 8 hours in group K.

Discussion

Prevention of hemodynamic instabilities like hypertension and tachycardia following noxious stimuli in neurosurgical patients is of extreme importance to a neuronanesthesiologist. As these hemodynamic perturbations affect the cerebral physiology and, thus, the outcome of the patients. The SNB is a regional analgesia strategy for supratentorial neurosurgery to provide hemodynamic stability and analgesia. The addition of adjuvants to local anesthetics has been shown to produce early onset and prolong the duration of analgesia. Several studies to date have tested the efficacy of scalp block

Table 3 Comparison of mean arterial pressure (MAP, mm Hg) at different time intervals between groups K and S

Perioperative mean arterial pressure (mm Hg)	Group K ($n = 30$)	Group S ($n = 30$)	*p*-Value
At baseline	86.27 ± 8.46	86.43 ± 7.92	0.937[a]
1 minute after induction	85.6 ± 6.55	84.3 ± 7.58	0.48[a]
5 minutes after induction	84.03 ± 5.59	83.47 ± 9.35	0.776[a]
During head pinning	86.4 ± 7.37	82 ± 12.67	0.107[a]
At skin incision	86.07 ± 7.38	81.67 ± 11.75	0.089[a]
60 minutes after incision	85.53 ± 6.38	82.13 ± 11.8	0.172[a]
During skin closure	79.4 ± 4.12	87.17 ± 12.67	**0.002**[a]
Extubation	78.4 ± 6.42	86.6 ± 13.31	**0.003**[a]
1 hour postextubation	80.13 ± 6.98	88.6 ± 13.1	**0.002**[a]
2 hours postextubation	84 ± 7.69	91.33 ± 10.51	**0.003**[a]
4 hours postextubation	86.2 ± 6.5	92.67 ± 12.61	**0.015**[a]
8 hours postextubation	85.4 ± 6.42	92.8 ± 13.31	**0.008**[a]
16 hours postextubation	84.13 ± 6.98	93.1 ± 13.1	**0.0016**[a]
24 hours postextubation	84.27 ± 6.13	88.1 ± 8.47	**0.049**[a]

[a]Independent *t*-test.

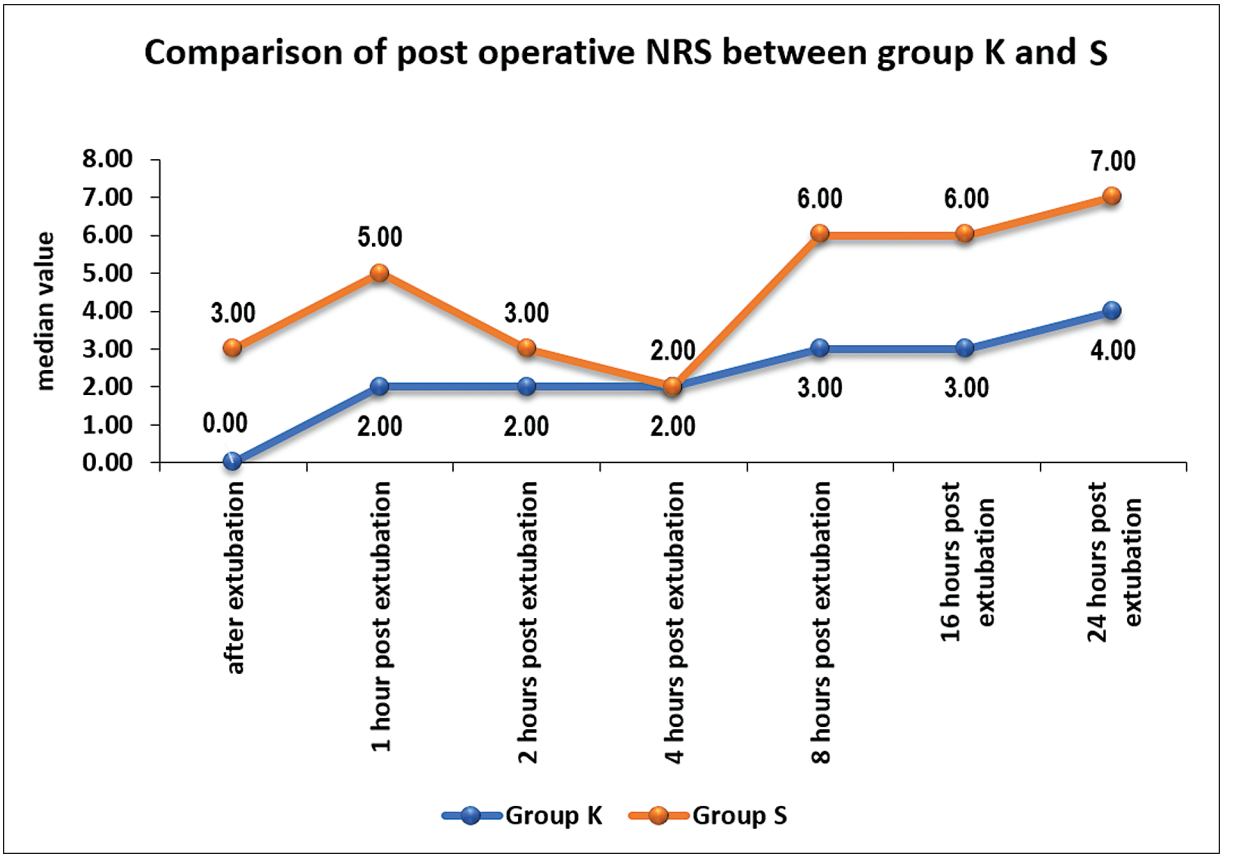

Fig. 2 Comparison of trend of postoperative numeric rating scale (NRS) at different time intervals between group K and S.

with local anesthetics alone or along with adjuvants like opioids, dexamethasone, clonidine, adrenaline, and dexmedetomidine for the same.[2,7,9,17–21]

Ketamine is an intravenous induction agent with LA activity and thus affects nerve conduction significantly. It is an NMDA receptor antagonist with reported central, regional, and LA and analgesic properties. It is, however, less commonly used in neurosurgery due to its effect on the cardiovascular system, namely, tachycardia and hypertension, which may adversely affect the patient with preexisting

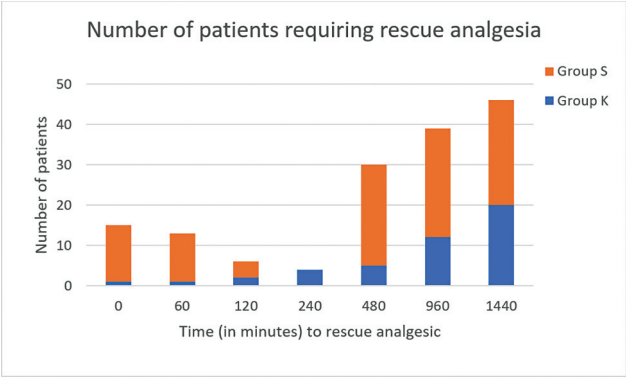

Fig. 3 The number of patients in each group requesting for rescue analgesic at different time points during the postoperative period.

raised ICP. Conventionally, it has been used as an adjuvant in various peripheral nerve blocks like brachial plexus block, femoral nerve block, etc., and has been shown to increase the duration of analgesia of the blocks without having adverse systemic effects.[14,22]

To the best of our knowledge, this is the first study that has compared bupivacaine alone and bupivacaine-ketamine combination for scalp block. The present study demonstrates that the addition of ketamine to bupivacaine for scalp block has improved hemodynamic profile perioperatively and provides better pain relief. It increases the duration of postoperative analgesia and decreases the need for opioids.

Acute increases in blood pressure and HR can be deleterious in neurosurgical patients, especially those with increased ICP. In such patients, these acute changes can cause a further rise in the ICP which may result in herniation and also systemic effects like the development of neurogenic pulmonary edema.[23] The use of scalp block in our study resulted in stable hemodynamics throughout the intraoperative period in both groups, except at the time of closure. This difference between the two groups continued in the postoperative period as well and was found to be statistically significant. Similar to our study, Stachtari et al, who compared the addition of dexmedetomidine to bupivacaine for scalp block, also observed significantly higher HR and blood pressure during dural closure in the group which received bupivacaine alone.[19] In another study by Hwang et al, conducted on aneurysm patients, stable intraoperative hemodynamics were reported along with reduced opioid requirement, as observed in our study.[24]

The median total opioid (fentanyl) consumed during the intraoperative period in group K was 200 mcg, while that in group S was 300 mcg (p-value < 0.0001). Reduced opioid consumption perioperatively has been reported by various studies on scalp block's effect on postcraniotomy pain previously. A meta-analysis conducted by Guilfoyle et al, concluded that there was a significant reduction in 24-hour opioid consumption in patients who received regional scalp block for craniotomy. In the same analysis, it was also observed that pain scores were reduced up to 12 hours in patients receiving scalp block with adjuvants like epinephrine.[4] Similarly, our study also reports better pain relief in patients belonging to group K, where ketamine was added as an adjuvant.

The pain scores in the postoperative period were found to be significantly lower in patients of group K as compared to group S in our study. Similar results have been shown by other studies where adjuvants like dexmedetomidine, fentanyl, and adrenaline have been added to the scalp block. The analgesic consumption by the patients in the postoperative period was also significantly reduced in the patients of group K as compared to group S. The first dose of rescue analgesia was administered immediately after extubation to 14 (50%) patients in group S, while only 1 (3.4%) patient asked for analgesia in group K. By the end of 2 hours all the patients of group S had received their first dose of rescue analgesic as opposed to 4 patients from group K, p-value < 0.00001. A study by Anyapu et al comparing the addition of fentanyl and dexmedetomidine to scalp block also revealed that the duration of analgesia was prolonged in both the groups with adjuvants, although more in the dexmedetomidine group than the fentanyl group.[25]

Our study also revealed higher NRS scores in the group S patients even 24 hours after surgery as compared to group K patients, who were relatively pain-free. This finding is in contrast with Stachtari et al, who have reported comparable visual analog scale scores between patients receiving scalp block with bupivacaine alone and those with dexmedetomidine added as an adjuvant.[19] This difference probably warrants a further study comparing ketamine with dexmedetomidine as a block adjuvant to understand its effect on the duration of analgesia.

No adverse events were reported in either of the groups in our study. There were no episodes of tachycardia or hypertension requiring intervention in the patients of group K. In a study conducted by Abdelhamid et al in patients undergoing modified radical mastectomy, ketamine was administered as an adjuvant for serratus anterior plane block, and the HR and blood pressure throughout the surgery were found to be comparable with baseline in all the patients.[26] Ketamine has been avoided so far in neurosurgeries because of its effect on HR and blood pressure and elevation in ICP. None of the patients in our study had features suggestive of raised ICP intraoperatively, and the brain relaxation scores, as described by the surgeon, were also comparable in both the groups (median score in both the groups was 2 with IQR 2-2 in group K and 1-2 in group S, p-value 0.083). A study conducted by Bhaire et al in neurosurgical patients to analyze the effect of the combination of ketamine and propofol on cerebral oxygenation also did not reveal any significant difference between the two groups in relation to the brain relaxation scores.[27]

Our study has a few limitations, like a small study sample, single-center study, and lack of block being provided by a single anesthesiologist. This study shows a potential benefit of the addition of ketamine as an adjuvant to scalp block by providing better pain relief and reduced opioid consumption, thus providing better postoperative care; however, further research with large sample size and comparison with other adjuvants like dexmedetomidine, clonidine, and epinephrine

is warranted to formulate a clinical practice for better patient care and reduced morbidity.

Conclusion

This study demonstrates that adding ketamine as an adjuvant to bupivacaine for scalp block not only provides significant hemodynamic stability but also reduces both intra- and postoperative analgesic consumption in patients undergoing craniotomy for supratentorial glioma.

Note
This manuscript was first presented at the ASNACC-2023 virtual conference, which convened from February 23rd to 25th, 2023.

Conflict of Interest
None declared.

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