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A prospective randomized study to compare hemodynamic changes and post-operative outcome of intravenous buprenorphine versus epidural buprenorphine in patients undergoing abdominal surgeries under general anesthesia

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ABSTRACT

Background: Post-operative pain following major abdominal surgeries is accompanied with multitude of negative consequences, including increased morbidity, impaired physical function, and slow recovery. Opioids are the gold standard of post-operative pain management. Buprenorphine is a new semi-synthetic opioid and 0.3 mg has shown equipotent effect as 12.5 mg of morphine and 0.125 mg of fentanyl. **Aims and Objectives:** The aims of this study were to compare the effects of epidural and intravenous buprenorphine and clinically significant differences on perioperative hemodynamic variables, duration, and quality of analgesia and its adverse-effects. **Materials and Methods:** A total of 60 patients with ASA grade I/II scheduled for elective abdominal surgeries under general anesthesia were randomized into two groups. Group IA received intravenous Inj Buprenorphine 0.3 mg diluted with 10 mL of normal saline and 10 mL NS given epidurally just before the closure of peritoneum; Group EA received epidural Inj Buprenorphine 0.3 mg diluted with 10 mL of normal saline and 10 mL NS given intravenously just before the closure of peritoneum. The post-operative hemodynamic vitals, analgesia, and adverse-effects were assessed at certain intervals over 24 h. **Results:** In both groups, there was a significant reduction in heart rate and blood pressure as compared to baseline (pre-induction) over first 2 h–3 h following the administration. Group EA has shown to provide satisfactory, prolonged duration of analgesia 22.32 h, and better visual analog scale score as compared to Group IA 18.71 h. **Conclusion:** Epidural buprenorphine 0.3 mg has proved to provide higher satisfactory post-operative analgesia and considered a better alternative to 0.3 mg intravenous buprenorphine in terms of prolonged post-operative analgesia and acceptable adverse event profile.

Key words: Buprenorphine; Epidural; Intravenous

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INTRODUCTION

Post-operative pain is one of the main adverse outcomes following major surgeries. Inadequate management of post-operative pain leads to significant negative consequences such as increased morbidity, prolonging stays in ambulatory care units, development of chronic pain, prolonged use of opioids, and impairs quality of life.[1,2] Multimodal analgesia is currently recommended for effective post-operative pain control which is achieved by combining different analgesics or administering the drug by different routes.[2] Opioids are the most effective analgesics for moderate to severe post-operative pain, which are mediated through specific receptors in the CNS that attenuates pain-related signals. Buprenorphine, a high potent lipophilic opioid which has partial agonist activity at mu, delta receptors and antagonist activity at kappa receptor.[3]

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Hence, it has been found to provide excellent analgesia in low dosage with less adverse effects than other opioids.[4] Epidural opioid administration has shown to provide better quality of analgesia during the first 3 days with less pulmonary complication than intravenous route.

The primary objective of our study was to compare the efficacy of buprenorphine for post-operative analgesia by administrating through two different routes and with secondary objectives to assess its hemodynamic outcomes and untoward side effects.

Aims and objectives

To compare the efficacy of intravenous and epidural buprenorphine in terms of postoperative hemodynamic variable, analgesia, its untoward side effects.

MATERIALS AND METHODS

This prospective, double blinded, and randomized controlled study was conducted after obtaining approval from the Institutional Ethics Committee (70/IEC-GRMC/2020 dated May 02, 2021) and registration with the Clinical Trial Registry-India (CTRI/2022/10/046510). The present study was conducted on a sample of 60 ASA grade I and II patients between 18 and 60 years of age undergoing abdominal surgeries under general anesthesia at Gajra Raja Medical College and J.A. Group of Hospitals, Gwalior, MP.

Patients who were uncooperative or not able to understand pain assessment test, history of any significant neurological, pulmonary, cardiovascular, hepatorenal, psychiatric or metabolic disease, bleeding diathesis, allergy or any other reaction to the study drug, parturient, and lactating women were excluded from the study.

All 60 patients satisfying the inclusion criteria were investigated for routine baseline pre-operative investigations. Two investigators were participated in the study, first investigator prepared the drug and second investigator did monitoring and data collection. Patients were randomized into two groups using sealed envelope method.

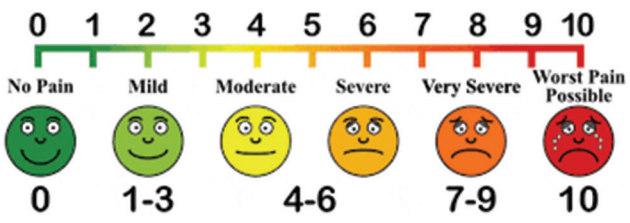
Group IA: Received intravenous Inj Buprenorphine 0.3 mg diluted with 10 mL of normal saline and 10 mL NS given epidurally just before the closure of peritoneum

Group EA: Received epidural Inj Buprenorphine 0.3 mg diluted with 10 mL of normal saline and 10 mL NS given intravenously just before the closure of peritoneum.

The night before surgery, patients were instructed to describe pain on visual analog scale (VAS). On the day of surgery, standard monitoring including electrocardiogram, oscillometric blood pressure, SpO_2, and end tidal CO_2 was recorded. Before induction, the patients were placed in sitting position. Under all aseptic precautions, a skin wheal was raised in the L1-2 or L2-3 inter-vertebral space with 2 mL of 2% lignocaine. An 18 gauge Tuohy needle was introduced through space around 1 cm and stylet was removed; a 10 mL loss of resistance (LOR) syringe with 5 mL of 0.9% normal saline was firmly fixed to the hub of the Tuohy needle. The needle was slowly advanced until it entered the epidural space which was identified by the LOR technique, the epidural catheter was threaded cephalad with 5–6 cm into the epidural space. Three milliliters of 2% lignocaine with epinephrine 1:200,000 was injected as a test dose. Segmental anesthesia was confirmed by the pinprick method 20 min after the epidural injection. All the patients were pre-medicated with Inj. Glycopyrrolate 0.2 mg IV slowly, Inj. Midazolam 1 mg IV, and Inj. Pentazocine 0.5 mg/kg IV as an analgesic in both groups. Anesthesia was induced with Inj. Thiopentone 5 mg/kg. Tracheal intubation was facilitated with Inj. Succinylcholine 2 mg/kg and with appropriate size endotracheal tube. Patients were maintained with nitrous oxide+oxygen (67:33) along with inhalation anesthetic agent (Isoflurane) of 0.5% to prevent awareness with controlled ventilation. Inj. Atracurium was administered as necessary to maintain muscle relaxation. No adjuvant drugs, including epidural local anesthetics, were administered during surgery. Just before the closure of peritoneum, respective group of patients received the Inj. Buprenorphine 0.3 mg on desired route. Reversal of muscle paralysis was done with Inj. Neostigmine 2.5 mg+Inj. Glycopyrrolate 0.5 mg. All the patients were extubated and shifted to the recovery room. Various parameters such as pulse rate, systolic pressure, diastolic pressure, mean arterial blood pressure, respiratory rate, and SpO_2 were measured and recorded in all the patients at baseline, at induction, after intubation and at particular intervals over 2 h intraoperatively. Post-operative hemodynamic vitals and analgesia were assessed using a VAS at certain intervals over 24 h.

VAS score

Post-operative pain was assessed by VAS scale consisting of a 10 cm horizontal scale with gradations marked with "0" indicating no pain at all and 10 indicating the worst pain imaginable.



VAS score rating: 0=No pain, 1–3=Mild pain, 4–6=moderate pain, and 7–10=Severe pain. VAS score >3 was managed by inj. Tramadol 2 mg/kg i.v.in 100 mL normal saline as rescue analgesia to relieve the pain.

Time for first rescue analgesic

It refers to the period of time between the onset of the analgesia after administration of study drug and time when the patient first complained of pain, that is VAS score >3.

Statistical analysis was done using SPSS software after compiling data in suitable EXCEL spreadsheet. The qualitative data (VAS score) were denoted as number % and compared by Chi-square test. The quantitative data (hemodynamic variables) were denoted as mean±standard deviation and compared by Student's t-test. (P<0.05-statistically significant; P<0.01- statistically highly significant)

RESULTS

Demographic profiles of patients in both the groups were comparable with respect to distribution of gender, ASA physical status, and age. Mean age of the participants in group IA was 42.8±12.28 years and group EA was 43.13±14.35 years. The difference between groups was statistically insignificant (P>0.05) among the variables (Graph 1).

Hemodynamic variables: Pulse rate

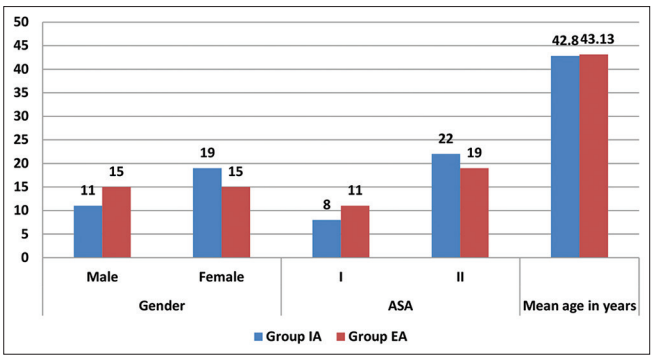
In both groups, there was significant reduction in heart rate as compared to baseline (pre-induction and intraoperative) over first 2 h–3h following the administration (Graph 2). Pulse rate differences were statistically significant between the groups at 120 min, 180 min, 12 h, and 24 h postoperatively (Graph 3). It is suggesting that buprenorphine was likely to cause bradycardia (10% reduction in heart rate).

Blood pressure

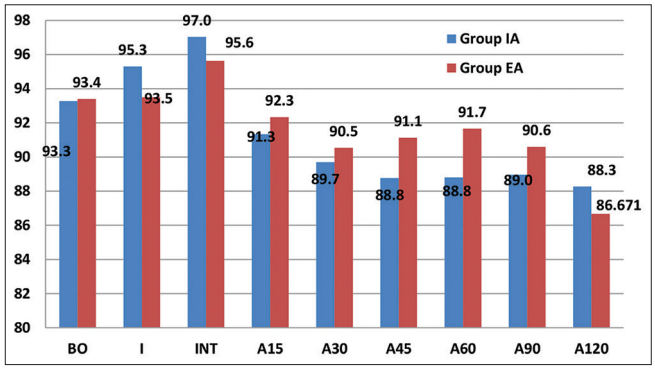
In both groups, there was significant reduction in blood pressure as compared to baseline (pre-induction and intraoperative, Graph 4) over first 2h-3h following the administration. Systolic blood pressure difference was statistically significant between the groups at 12 h postoperatively (Graph 5). There was no statistical significant difference in diastolic blood pressure and mean arterial blood pressure between groups postoperatively.

Respiratory function

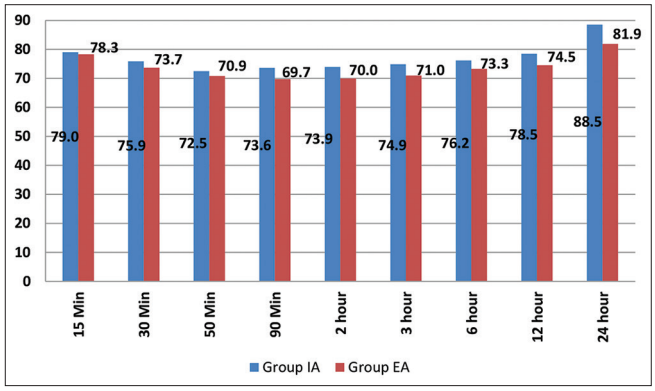
There were no statistically significance differences (P>0.05) among the study groups on mean SpO_2 and mean respiratory rate postoperatively.



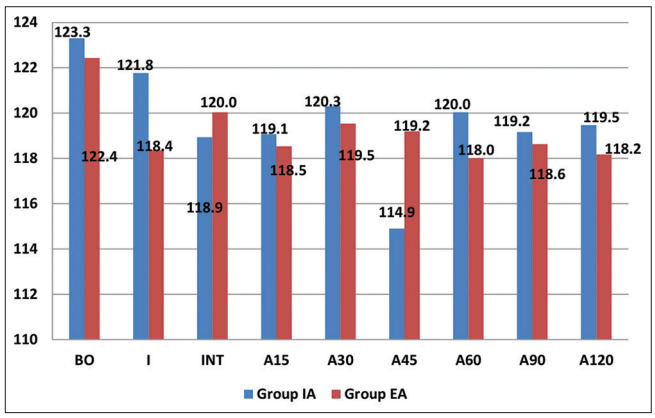
Graph 1: Demographic profile of study participants



Graph 2: Intraoperative pulse rate in the study participants



Graph 3: Post-operative pulse rate in the study participants



Graph 4: Intraoperative SBP in the study participants

Post-operative analgesia

VAS score

In both the groups, VAS score was lower in the early interval, that is, till 180 min postoperatively following which there was gradual increase in VAS score in Group IA as compared to Group EA and was statistically significance (P<0.05) at the interval 6 h, 12 h, and 24 h postoperatively among the study groups (Graph 6).

Duration of analgesia and time of rescue analgesia

Group EA provides prolonged duration of analgesia 22.32 h±1.57 (Mean+SD) as compared to 18.72 h±1.51 (Mean+SD) in Group IA. There was statistically highly significant difference (<0.01) in time of rescue analgesia between the study groups (Graph 7).

Adverse effects

The incidence of sedation was very common with intravenous buprenorphine as compared to epidural followed by hemodynamic complications such as bradycardia and hypotension. Other non-significant complications were nausea and shivering (Graph 8).

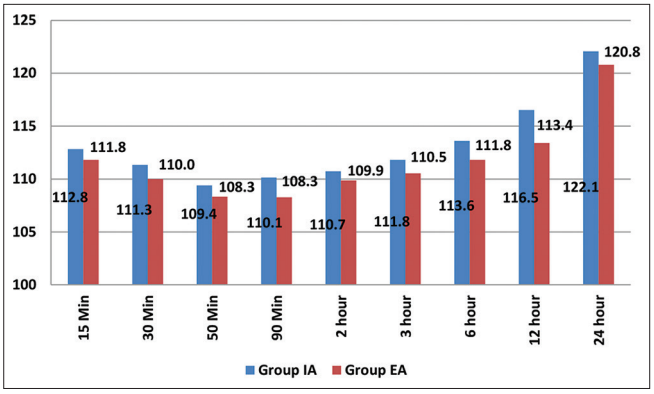
DISCUSSION

Despite recent advances like better understanding of pain mechanism, physiology, pharmacology, awareness of the postsurgical pain prevalence, and advances in pain management services, inadequately controlled post-operative pain still continues to be challenging health-care problem.[1,5]

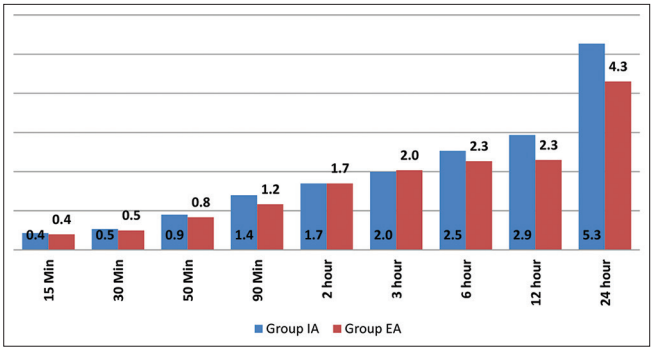
Buprenorphine is up-trending high potency opioid using nowadays, has shown to provide excellent analgesia in low dosage with less adverse effects than other opioids. Hence, we have studied the post-operative hemodynamic changes, analgesia, and adverse effects following the administration of Inj. Buprenorphine through two different routes (Epidural and intravenous).

In our study, intragroup pulse rate differences were statistically significant at 120 min, 180 min, 12 h, and 24 h postoperatively. There were statistically significant differences in intragroup systolic blood pressure at 12 h postoperatively and were statistically insignificant between groups in diastolic and mean arterial blood pressure postoperatively.

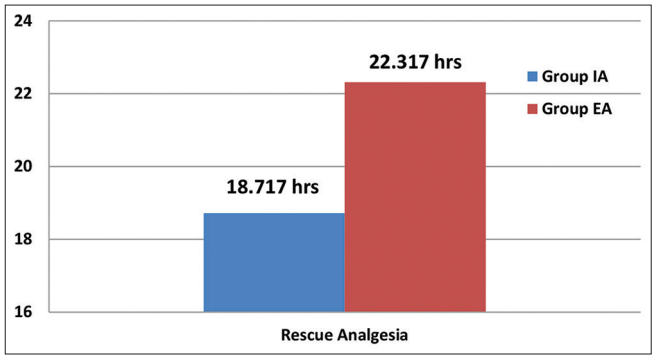
In both groups, there was significantly reduction in heart rate and blood pressure as compared to baseline (pre-induction) over first 2 h–3 h following the administration. Bradycardia (10% reduction in heart rate) may be attributed to the effect of buprenorpine due to its mu receptor agonist mediated attenuation of baroreceptor reflex. Similar findings have been reported in other several studies.[6-9]



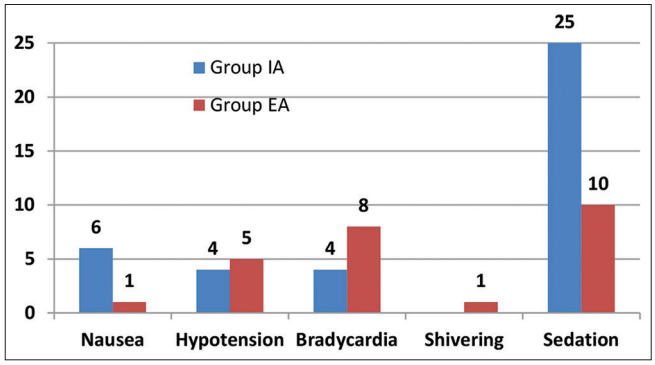
Graph 5: Post-operative SBP in the study participants



Graph 6: VAS score in the study groups



Graph 7: Time to rescue analgesia in the study groups



Graph 8: Post-operative complications in the study groups

There were no statistically significant differences between the study groups on respiratory rate and SpO_2. There were no instances of respiratory depression in this study. Similar trend was reported by Gupta et al.[7]

Both groups have shown lower VAS score in early intervals, over 180 min postoperatively following which slow increase in VAS score in intravenous groups as compared to epidural. VAS score was comparatively less and satisfactory with epidural buprenorphine and was statistically significant between the groups at 6 h, 12 h, and 24 h. It was supported by Inagaki et al.[10]

Epidural buprenorphine has provided prolonged duration of analgesia 22.32 h±1.57 (Mean±SD) as compared to 18.72 h±1.51 (Mean±SD) in intravenous buprenorphine. There was statistically highly significant difference (<0.01) in time of rescue analgesia between the groups. Prolonged duration of analgesia and long-lasting efficacy of buprenorphine are due to higher partition co-efficient, high lipid solubility allows more diffusion into spinal cord and brain and high affinity to mu receptor and its slow dissociation.[3,7,10-13,17,18] Similar findings have been reported by other studies.[6,7,11] In this study, most commonly observed adverse effect was sedation, 25 (83.3%) patients in Group IA, and 10 (33.3%) in Group EA. It may be by the slow dissociation property of mu receptor or some studies supported that due to kappa receptor agonist property.[12,13] Similar trend was observed by other studies.[3,10,14]

Other side effects were bradycardia 8 (26.7%) patients in Group EA and 4 (13.3%) in Group IA; hypotension 4 (13.3%) in Group IA and 5 (16.7%) in Group EA. It may be due to additional autonomic response suppression property of buprenorphine; similar finding has been reported by Kay,[15] Nishikawa et al.,[16] Other non-significant side effects were nausea shivering.

Limitations of the study

It was a mono-centric study; external validity might have been compromised.

CONCLUSION

The present study established the effectiveness of buprenorphine and its routes (epidural and intravenous) in post-operative pain relief following abdominal surgeries under general anesthesia.

It has shown that the duration of analgesia was found considerably prolonged when buprenorphine was used through epidural route compared with intravenous route. The use of buprenorphine through intravenous route was found to be associated with a considerable higher VAS scores and higher incidence of bradycardia in the late post-operative period compared with those receiving buprenorphine through epidural route.

It can be concluded that 0.3 mg epidural buprenorphine is a better alternative to 0.3 mg intravenous buprenorphine in view if considerably prolonged post-operative analgesia and acceptable adverse event profile.

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YM- Concept, literature survey, intellectual contents, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **JA-** Concept, design, clinical protocol, manuscript preparation, editing, manuscript revision and supervision; **BK-** Data collection, coordination and preparation of manuscript; **SS-** Design of study, statistical analysis and interpretation, manuscript review; **PG-** Proof-reading and revision of manuscript.

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