Original Research Article

Prophylactic use of intraoperative Nor-epinephrine infusion vs. bolus doses of Ephedrine and Phenylephrine in patients undergoing colorectal surgery under combined general and epidural anaesthesia for enhanced recovery after surgery. (ERAS)

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Abstract

Introduction*:* Enhanced recovery after surgery (ERAS) has become an important focus of perioperative management after colorectal surgery. Maintenance of arterial blood pressure during combined general and epidural anesthesia is essential for organ perfusion and has been found as an important prognostic factor for enhanced postoperative recovery. **Aim**: To compare Norepinephrine infusion with ephedrine / phenylephrine boluses to maintain stable blood pressure and enhance postoperative recovery. **Methods:** Patients with physical status ASA I and II of either sex admitted for colorectal surgery were randomized into two groups. Group A: Nor-epinephrine group and Group B: Ephedrine/Phenylephrine group. After induction of general anesthesia Group A patients received norepinephrine infusion at a dose to keep mean arterial pressure (MAP) more than or equal to 80 mmHg after epidural anesthesia was activated with 10 ml of 0.25% ropivacaine whereas Group B patients received Ephedrine / Phenylephrine stat doses in case of hypotension (MAP < 80 mmHg) during intraoperative period. Intraoperative hemodynamics and fluid input output were recorded in both groups. Post operative hemodynamics, renal function, oral feeding and early mobilization were compared in both the groups as indicators of enhanced recovery. **Results:** Prophylactic use of Norepinephrine infusion in patients undergoing colorectal surgery under combined epidural and general anesthesia was found to produce more stable intraoperative blood pressure compared to the use of ephedrine/phenylephrine boluses. Fluid requirement in group A during the procedure was less as compared to group B and the urine output during intraoperative period was better in patients receiving nor epinephrine infusion . Postoperative complications were lower in patients receiving norepinephrine infusion. **Conclusion:** Prophylactic use of nor epinephrine infusion to prevent intraoperative hypotension in patients undergoing colorectal surgery under combined epidural and general anesthesia was found to produce more stable intraoperative blood pressure and better postoperative course .

Keywords: Epidural, norepinephrine, colorectal.

Introduction

Epidural anesthesia is an important component of anesthesia in major abdominal surgeries. Role of epidural has increased with the concept of Enhanced Recovery Protocol. Enhanced recovery after surgery (ERAS) or "fast-track" programs have become an important focus of perioperative management after colorectal surgery[1,2]. Epidural and non-opioid analgesia is one of the key principles of ERAS. A common physiological effect of epidural and spinal anaesthesia is hypotension, primarily due to blockade of the sympathetic nervous system causing arterial and venous vasodilatation with subsequent "functional" hypovolemia[3].

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Maintenance of arterial blood pressure is essential for organ perfusion. Tissue hypo perfusion leads to a systemic inflammatory response syndrome which is a key determinant of postoperative complications. Persistent intraoperative hypotension has been reported as an important prognostic factor of postoperative morbidity and mortality[4].

Materials and methods

This prospective observational study was conducted in the Department of Anaesthesiology at Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India from 2018 to 2021, after proper ethical clearance from the institutional ethical committee. Patients with physical status ASA I & II of either sex admitted for elective colorectal surgery were included in the study.

Exclusion criteria

- Patient refusal for the study.
- Deformity of spine
- Allergy to local anesthetics
- Coagulopathy
- Advanced Hepatic, Cardiac & Renal impairment

At the pre-operative visit, all the patients were evaluated and assessed a day before the procedure. The participating patients were randomized into two groups:

Group A: Nor-epinephrine infusion group

Group B: Ephedrine/Phenylephrine group

All the patients received a balanced salt solution as maintenance from midnight according to the body weight. Patients were assessed on arrival to the operating room and base line vitals HR, NIBP & SpO_2 were recorded. All patients were given a 500 ml bolus of Hydroxyethyl starch on arrival. Epidural catheter was placed at T10 in lateral position under aseptic technique. Test dose of 3ml of 2% lignocaine with epinephrine (5µgm/ml) was given. Epidural catheter placement was followed by general anesthesia with endotracheal intubation using propofol and rocuronium. All patients had an intra arterial cannula for blood pressure monitoring.

Group "A" patients received norepinephrine infusion (40mcg/ml) at a dose to keep MAP ≥ to 80 mmHg immediately after epidural anaesthesia was activated with 10 ml of 0.25% ropivacaine whereas Group "B" patients received Ephedrine(6mg)/Phenylephrine (50mcg) stat doses in case of hypotension (MAP < 80 mmHg) during intra operative period. Phenylephrine was given to the patients with tachycardia and hypotension. Epidural infusion of ropivacaine 0.2% was continued at 5ml per hour in both groups till end of surgery.

Heart rate, blood pressure and SpO_2 were recorded intra operatively and continued for 72 hrs postoperatively (4hrly).

Following parameters were compared in both the groups:

1. Intra operative Blood pressure
2. Intraoperative Heart rate
3. Fluid intake in the intraoperative period
4. Intraoperative Urine output
6. Postoperative renal function
7. Early mobilization
8. Feeding.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean ± SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar diagrams. Student's independent t-test or Mann-Whitney U-test, whichever feasible, was employed for comparing continuous variables. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. A P-value of less than 0.05 was considered statistically significant.

Results

Demographic parameters (age, sex, diagnosis) were comparable between the two groups. Majority of the cases in both the groups were Ca Rectum (60%) followed by Ca Colon (19%). Most of the procedures in both groups included LAR and hemicolectomies(figure 1)

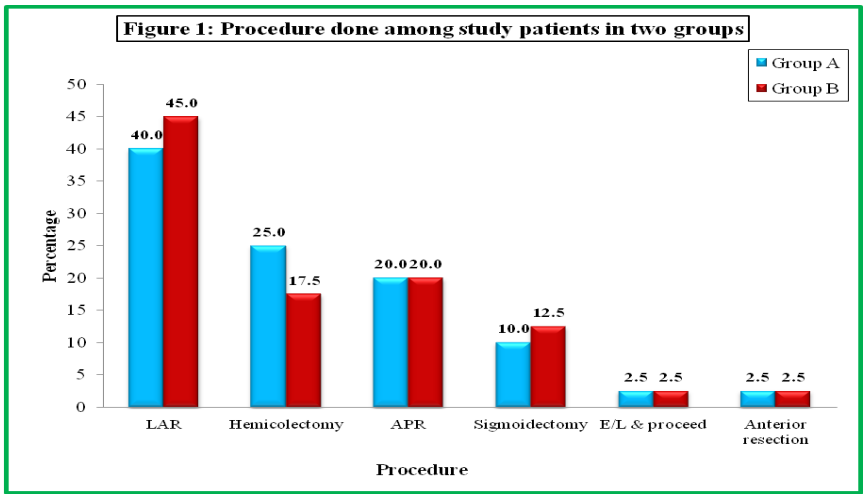

Fig 1:Procedure done among study patients in two groups

There was significant difference in Heart Rate ($p<0.05$), Mean Arterial pressure ($p<0.05$) in both the groups intraoperative (Table 1) with lower heart rate and higher blood pressure values in group A.

Table 1. Comparison based on intraoperative vitals in two groups

Parameter	Group A		Group B		P-value
	Mean	SD	Mean	SD	
HR (beats/min)	89.4	6.43	97.0	9.69	<0.001*
SBP (mmHg)	117.0	3.77	111.2	2.92	<0.001*
DBP (mmHg)	75.0	3.36	68.3	2.48	<0.001*
MAP (mmHg)	89.0	2.84	82.6	2.18	<0.001*
SpO_2 (%)	99.1	0.99	99.4	0.98	0.175

Total fluid intake during intraoperative period in Group A was having mean value of 2.54 liters whereas in Group B it was 3.91 liters. ($p<0.001$)

Urine output was having mean value of 856.3 ml during intraoperative period in Group A whereas in Group B it was 510.2 ml ($p< 0.05$)

Difference in both the groups with respect to Mean Arterial pressure on 1st 2nd & 3rd POD was statistically significant (Table 2)

Table 2.Comparison based on postoperative mean arterial pressure in two groups

MAP (mmHg)	Group A		Group B		P-value
	Mean	SD	Mean	SD	
1st POD	92.56	5.31	85.00	5.00	<0.001*
2nd POD	92.07	3.49	87.03	3.89	<0.001*
3rd POD	93.07	3.92	88.47	2.77	<0.001*

Group A patients mobilized early and had faster return to oral feeding as compared to group B.
Mean number of days till mobilization in Group A were 2.4±0.501 whereas Group B was having mean value of 3.2 ± 0.984 days (p<0.05). (Table 3)

Table 3.Comparison based on early mobilization in two groups

Early mobilization	Group A		Group B		P-value
	No.	% Age	No.	%Age	
2nd POD	23	57.5	13	32.5	<0.001*
3rd POD	17	42.5	10	25.0	
≥ 4th POD	0	0.0	17	42.5	
Total	40	100	40	100	
Mean ± SD (Range)	2.4 ± 0.501		3.2 ± 0.984		

Mean number of days till start of oral feeding in Group A was 1.5 ± 0.553 whereas in Group B it was 2.6 ± 1.395. (p<0.05) Table 4

Table 4.Postoperative oral feeding in two groups

Postoperative oral feeding	Group A		Group B		P-value
	No.	%Age	No.	%Age	
1st POD	21	52.5	11	27.5	<0.001*
2nd POD	18	45.0	8	20.0	
3rd POD	1	2.5	15	37.5	
≥ 4th POD	0	0.0	6	15.0	
Mean ± SD	1.5 ± 0.553		2.6 ± 1.395		

Patients in group B had elevated renal parameters in postoperative period as compared to group A.
Mean values of Urea in mg on 1st, 2nd & 3rd POD were 20.56, 20.35, 20.17 in group A whereas in Group B, values were 33.05, 33.45, 33.00. (p<0.05)
Mean value of Creatinine in mg on 1st, 2nd & 3rd POD were 0.92, 0.90 & 0.91 in group A whereas in Group B, values were 1.13, 1.10, 1.05. (p<0.05)

Discussion

Intraoperative hypotension (IOH) is a common and frequent side effect of anaesthesia[5]. Borghi et al found that 61% of the patients developed hypotension under combined general and epidural anaesthesia, whereas 23% of the patients developed IOH under general anaesthesia only and 18% of the patients developed IOH under epidural anaesthesia alone[6]. Elevated risk of end organ injury was reported for exposures to mean arterial pressures <80 mm Hg for greater than 10 min and < 70 mm Hg for shorter duration. There is a high incidence of myocardial damage after intraoperative reduction in systolic blood pressure more than 50% from baseline lasting more than 5 min[7]. Acute Kidney Injury is also one of the worst outcomes due to intraoperative hypotension. Postoperative delirium and cognitive dysfunction are also complications of intraoperative hypotension (MAP < 50mm Hg)[8]. It is a common practice to infuse large volumes of crystalloid solution rapidly to prevent or to treat hypotension induced by spinal or epidural block. This increases the venous return and therefore the cardiac output, which in turn will improve peripheral circulation, however at the expense of affecting oxygen delivery[9].
Sympathetic blockade produced by spinal and epidural blocks can be corrected by the use of vasoconstrictor agents. Ephedrine is often used to treat acute decrease in blood pressure, particularly in patients with bradycardia. Administration of ephedrine boluses can lead to prolonged exposure of patients to hypotension. Ephedrine cannot be administered as a continuous infusion. Phenylephrine is often selected to treat hypotension if normal or elevated HR is present. Recent experimental data have shown that continuous infusion of norepinephrine can be used to prevent intraoperative hypotension by causing less cardiac depression[10]. Main advantage of giving a drug by intravenous infusion allows precise control of plasma drug concentrations to fit the individual needs of the patient and duration of drug therapy can be maintained or terminated as needed. So far, many studies have been conducted on the comparison of drugs for intraoperative low blood pressure[11]. However in our study we used prophylactic norepinephrine infusion to prevent hypotension under combined epidural and general anaesthesia in patients undergoing colorectal surgery. We used a manually controlled infusion using a simple algorithm.
In our study, we included a control group that didn't receive any prophylactic vasopressor. In this group rescue boluses of ephedrine/phenylephrine were given as required to treat any episodes of hypotension that occurred.
Mean intraoperative Heart Rate in Group A was lower (89.4 beats/min) than in Group B (97 beats/min) and the difference was statistically significant. Hassani et al[12] compared Ephedrine vs Norepinephrine in treating anaesthesia induced hypotension in hypertensive patients, and found that heart rate at the end of anaesthesia was lower in the norepinephrine group. Mean Systolic blood pressure, Diastolic blood pressure and Mean arterial pressure were higher in Group A as compared to Group B during intraoperative as well as postoperative period and the differences were significant. Our results were similar to Elraziq et al[13] who found that norepinephrine had faster onset with rapid and superior hemodynamic stability compared to ephedrine by maintaining stable blood pressure and heart rate. Ngan Kee et al[14] compared the prophylactic norepinephrine infusion versus boluses given to treat hypotension in cesarean section patients. The results showed the superiority of norepinephrine infusion over the intermittent boluses as regard to hemodynamic stability.
Shafei et al[15] showed that norepinephrine is effective in maintaining systolic blood pressure with reduction in heart rate, which is useful in coronary disease patients. Vallee et al[16] assessed the effect of norepinephrine and phenylephrine boluses to treat hypotension during maintenance anaesthesia, assessing MAP, derived cardiac output and arterial stiffness parameters and suggest that low dose of nor epinephrine could represent a highly conceivable alternative to treat general anaesthesia induced arterial hypotension.
It was suggested by Chapell et al[17] that the intraoperative strategy of using a continuous low dose infusion of Norepinephrine could improve the prognosis of the patient by reducing intraoperative fluid loading during major surgery. In our study we also found that the total fluid intake in Group A patients was lesser as compared to Group B patients with a statistically significant difference. It was also found that intraoperative urine output in Group A was more as compared to Group B. This may be because of the reduced renal perfusion and prolonged hypotension in Group B patients during intraoperative period.
In our study it was found that patients of Group A started mobilization earlier with a mean value of 2.4 ± 0.5 days as compared to Group B with mean value of 3.2 ± 0.9 days. Early mobilization is

the key element of enhanced recovery after surgery. Intraoperative hypotension and liberal fluid intake lead to increased postoperative organ dysfunction i.e AKI, ARDS, sepsis, myocardial infarction, postoperative delirium, delayed wound healing & postoperative ileus that leads to delayed mobilization and prolonged hospital stay. Our results were similar to Fabian Grass et al[18] who found that fluid overload was independent risk factor for delayed mobilization, which was associated with increased postoperative complications

Tassoudis et al[19] observed that persistent hypotension during elective major abdominal surgery is a significant risk factor for postoperative complications and may prolong hospitalization and effect patient outcome. Total hypotension time was an isolated factor significantly associated with morbidity and significantly prolonged hospital stay. Mean time to start oral feeding in Group A was 1.5 ± 0.55 days as compared to 2.6 ± 1.39 days in Group B. The difference between the two groups was statistically significant. Delay in feeding in Group B is due to postoperative complications. Bowel edema secondary to volume overload is associated with delayed recovery of gastrointestinal function and extended hospital stay. Our results were similar to Matthew et al[20] who found that in patients undergoing rectal cancer operation, increasing volume of crystalloid fluid administration was associated with higher incidence of postoperative ileus. Our results are similar to Futier et al[21] who observed that patients receiving prophylactic norepinephrine infusion for hemodynamic stability had less risk of renal dysfunction as compared to the patients receiving standard treatment i.e ephedrine boluses. Figure 2 below depicts post operative craetinine values in the two groups.

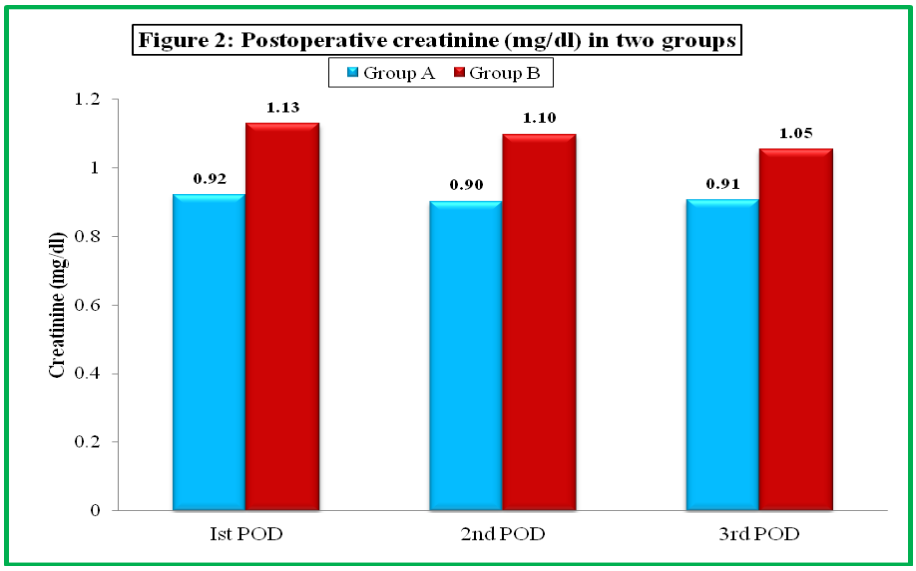

Fig 2:Postoperative creatinine (mg/dl) in two groups

Sun et al[22] demonstrated that postoperative AKI was associated with sustained intraoperative hypotensive periods of MAP of 55-60mmHg. AKI was associated with MAP less than 60 mmHg for 11-20 min and MAP less than 55 mmHg for more than 10 minutes in a graded fashion. We used a higher threshold for MAP to avoid the associated risks with lower MAP. Norepinephrine infusion, although at a low dose was infused through a large bore peripheral line as putting central line for the infusion was considered unnecessary.

Conclusion

Prophylactic use of norepinephrine infusion to prevent intraoperative hypotension in patients undergoing colorectal surgery under combined epidural and general anesthesia was found to produce more stable intraoperative blood pressure and better postoperative course compared to the use of ephedrine/phenylephrine boluses given at MAP<80 mmHg. Postoperative complications i.e delayed mobilization, gastrointestinal and renal dysfunction were lesser in patients receiving norepinephrine infusion along with restrictive fluid therapy.

Conflict of interest

None to be declared

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