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Original Research Article

Evaluation of Epidural Buprenorphine for Postoperative Analgesia for Below Umbilical Surgical Procedures

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ABSTRACT

Introduction: Epidural analgesia with local anaesthetics is extremely effective in controlling postoperative pain, but its use has been limited by concerns about possible hypotension, tachyphylaxis, systemic toxicity, technical difficulty with insertion of an epidural catheter and problems of postoperative surveillance. Addition of opiates to epidural local anaesthetic avoids many of these side effects. Buprenorphine, as an additive is attractive choice since it is not a controlled drug, has minimum addition potential, is marketed preservative-free and provides a long duration of action with minimum side effects. A prospective study was conducted to evaluate the efficacy of epidural buprenorphine for postoperative analgesia in patients undergoing surgical procedures below the umbilicus under epidural anaesthesia.

Materials & Methods: Sixty patients of either sex, 20-50 years of age, belonging to ASA grade I, undergoing surgical procedures below the umbilicus under epidural anaesthesia was randomly allocated to two groups of 30 patients each. Group I: Patients receiving only local anaesthetic epidurally. Group II: Patients receiving a combination local anaesthetic with buprenorphine, 3µg/kg body weight, epidurally, 15mins prior to surgery. Pulse rate, blood pressure, respiratory rate and pain scores were monitored. Incidence of side effects was noted.

Results: Buprenorphine, 3µg/kg, added to local anaesthetic provided good intensity and significantly longer duration of analgesia, as compared to the local anaesthetic group. The most common side effects observed were sedation and nausea and vomiting. While the degree of sedation which occurred was welcome, nausea and vomiting responded very well to anti-emetics.

Keywords: epidural analgesia, local anaesthetic, additive, opiates, buprenorphine

INTRODUCTION

Fear of pain during and after surgery is the main cause of reluctance for surgery in most patients. The advances made in the field of anaesthesiology have alleviated the former to a great extent, but the perfect solution to the problem of postoperative analgesia has largely eluded modern medicine. Postoperative pain relief significantly reduces physical morbidity following surgery, as well as the incidence of pulmonary complications, venous thrombosis and alterations in homeostatic mechanisms.

Any method of postoperative analgesia must meet three basic criteria- it must be effective, safe and feasible. The commonest hospital practice has been to prescribe a fixed parenteral dose of an opioid to be given at limited time intervals, with the administration of the same being delegated to a nurse. This method of pain relief has a lot of short-comings like discomfort of multiple injections and undesired side effects like nausea, vomiting,

dysphoria and respiratory depression. It may also result in urinary retention and may favour addiction.

Epidural analgesia with local anaesthetics is extremely effective in controlling postoperative pain, but its use has been limited by concerns about possible hypotension, tachyphylaxis, systemic toxicity, technical difficulty with insertion of an epidural catheter and problems of postoperative surveillance. Patient-controlled analgesia, though successful in overcoming these problems, requires sophisticated and relatively expensive apparatus.

Discovery of opiate receptors in the CNS, [1,2] in particular their existence in the spinal cord, [3] resulted in the use of various opioids for producing analgesia without loss of other sensations, with minimal CNS depression and without the unpleasant consequences of autonomic blockade. [4] Morphine was the most commonly used epidural opioid, producing long-lasting analgesia of good quality, but with a high incidence of serious side effects. Hence other opioids were suggested. The ideal opioid drug for epidural use should have the following characteristics:

-high lipid solubility, inducing fast diffusion into the neural tissues with little systemic absorption

-high molecular weight

-strong binding to receptor protein, thus producing prolonged effect

-intense and prolonged intrinsic activity

-nonaddicting and having less side effects, specially respiratory depression

Buprenorphine, a the baine derivative comes close to being an ideal opioid for epidural use as it is highly lipophilic, [5] has high receptor occupancy [6,7] and dissociates slowly from the receptor site. [8] In animal studies, it was found to have analgesic effect at least 35 times more potent than morphine. [9,10] Its depressant action on respiration is very weak. Also, it has a morphine antagonistic effect approximately three times stronger, and duration of action six times longer than naloxone.

The present study was undertaken to evaluate the efficacy of epidural buprenorphine for postoperative analgesia for surgical procedures below umbilicus and to study the incidence of adverse effects. Steps were taken to find out whether epidural buprenorphine possesses any extent of operative analgesia.

MATERIALS & METHODS

After obtaining approval from Institutional Ethics Committee, a prospective study was conducted to evaluate the efficacy of epidural buprenorphine for postoperative analgesia in patients undergoing surgical procedures below the umbilicus under epidural anaesthesia. A total of 60 patients of either sex, 20-50years of age, belonging to ASA grade-I, undergoing elective lower abdominal and inferior extremity surgery were taken up. Patients with signs and symptoms of respiratory, cardiovascular and neurological disorders and deformity of spine were excluded from the study.

Routine investigations like haemogram, blood sugar and serum creatinine, routine and microscopic examination of urine and chest X-ray were done. Special investigations like ECG were done in patients >40years of age and where deemed necessary. During the preoperative evaluation, the patients were explained regarding the anaesthesia procedure along with possible risks and complications and their consent was taken. The surgeons were also informed about the anaesthetic technique and the mode of postoperative analgesia.

Ten patients of either sex, posted for short surgical procedures below umbilicus, not lasting more than 30minutes, were randomly selected and administered buprenorphine epidurally (in a dose of 3µg/kg body weight diluted in 10ml Normal saline).After 15minutes, it was found that none of the patients had adequate operative

analgesia and had to be supplemented with general anaesthesia.

For the study, the patients were randomly allocated to two groups of 30 patients each as follows:

Group I: Patients receiving only **local anaesthetic** (a combination of 12ml of lignocaine 2% with adrenaline 1:200000 + 8ml of bupivacaine 0.5%) epidurally.

Group II: Patients receiving a combination of **local anaesthetic** (12ml of lignocaine 2% with adrenaline 1:200000 + 8ml of bupivacaine 0.5%) **with buprenorphine** 3µg/kg body weight, epidurally, 15mins prior to surgery.

No premedication was given either before surgery or on previous night, lest it may affect the assessment of postoperative analgesia.

After confirming NPO status, noninvasive blood pressure (NIBP) pulse oximeter (SpO_2) and ECG monitors were attached and pulse rate (PR), NIBP and respiratory rate (RR) were noted. An infusion of Ringer's lactate was started through an 18G cannula. Epidural block was performed at 2^{nd} or 3^{rd} lumbar interspace with the patient in lateral decubitus position. Epidural space was identified by 'loss of resistance' technique and the study drug (local anaesthetic or local anaesthetic with precalculated amount of buprenorphine) was administered at the speed of 1ml/second.

Failed or patchy blocks were excluded from the study. Intra-operatively, intravenous fluids were given at a rate of 10ml/kg/hr unless otherwise warranted by hypotension, in which case, the flow was increased to combat the fall in blood pressure. Severe and sustained fall in blood pressure over 30mmHg from preoperative value was treated with inj. ephedrine in 5mg increments. Inj. atropine was kept ready to be given only if PR fell below 60/min. The PR, NIBP and RR were recorded just after the block and every 5mins thereafter, till the end of surgery. Side effects, if any were noted.

During the postoperative period, PR, NIBP, intensity and duration of analgesia were monitored two hourly for the next 36hrs. The intensity of pain was assessed by Visual Analogue Scale (VAS) of 0 to 10, which had been explained to the patients in the preoperative visit. 0 to 3 was taken as mild pain, 3.1 to 7.5 as moderate pain and 7.6 to 10 as severe pain. The number of patients asking for postoperative analgesia was noted. Time to fifth demand made by each patient was used to obtain the duration of analgesia. The patients given analgesic supplementation were counted out of the study from that point onwards. Side effects were noted and treatment instituted, if necessary. The study was terminated after 48hrs.

The data obtained were subjected to statistical analysis by using paired student's t-test. A p value of less than 0.05 was considered to be significant.

RESULTS

A total of 60 patients were randomly allocated to two groups (30 in each group) to receive the following drugs:

Group I-- Local anaesthetic solution alone, epidurally.

Group II – Local anaesthetic solution with buprenorphine (3µg/kg), epidurally.

The parameters recorded were-

1. Type of surgery
2. Age, sex and weight of patients
3. Changes in pulse rate
4. Changes (fall) in systolic blood pressure
5. Changes in respiratory rate
6. Duration of postoperative analgesia
7. Pain scores at different times postoperatively
8. Number of patients requiring analgesic supplementation postoperatively and
9. Incidence of side effects.

Type of Surgery

All cases selected were of lower abdominal surgery or surgery on lower limbs. The number of patients scheduled for any particular type of surgery in each group, were comparable [Table **1**].

Table 1-Types of Surgery

Type of Surgery	Group I (n=30)	Group II (n=30)
Gynaecological	14	16
Plastic	2	0
Orthopaedic	6	7
Genito-urinary	5	2
General	3	5

Age and Sex of patients

All patients were between the age group 24-50years. The mean age of the patients in the two groups were comparable, as shown in Table **2**.

Table 2-Age and Sex Distribution

Age Group (years)	Group I		Group II	
	Male	Female	Male	Female
20-30	5	2	3	2
31-40	7	6	8	9
41-50	4	6	3	5
Mean age ± S.D	36.80 ± 8.41		37.23 ± 6.38	
Range of age	24-50		26-50	

Weight of patients

All patients weighed between 36-66kgs. The mean weight of the two groups was comparable (Table **3**).

Table 3- Weight of patients

Weight(kg)	Group I(n=30)		Group II(n=30)	
	Male	Female	Male	Female
<40	---	---	---	1
41-60	10	14	8	15
>60	6	---	6	---
Mean weight± S.D	53.07± 6.53		52.3± 7.27	
Range of weight	42-65		36-66	

Change in Mean Pulse Rate

In both the groups, there was an initial increase in the mean pulse rate at 15mins after the administration of the epidural block which tended to return to near preoperative values later on. The increase in pulse rate was not found to be statistically significant when compared group-wise (Table **4**).

Table 4 -Change in Mean Pulse Rate

Mean Pulse Rate	Group I(n=30)	Group II(n=30)
Pre-op	82.80 ± 5.89	83.8 ± 6.88
15 min after epidural	91.07 ± 6.60	93.93 ± 7.81
30 min after epidural	90.93 ± 5.53	90.67 ± 5.11
Immediate post-op	86.67 ± 4.48	86.93 ± 4.03

Change in Mean Systolic Blood Pressure

There was an initial fall in systolic blood pressure (SBP) from preoperative values at 15mins after the block in both the groups. At 30mins and later, the mean SBP tended to rise back to near preoperative values. When compared, the fall in mean SBP did not differ significantly in the two groups (Table-**5**).

Table 5 –Change in Mean Systolic Blood Pressure

Mean SBP	Group I(n=30)	Group II(n=30)
Pre-op	133.93 ± 11.9	132.80 ± 13.3
15 min after epidural	120.53 ± 11.3	118.40 ± 11.65
30 min after epidural	123.93 ± 8.6	125.53 ± 10.95
Immediate post-op	130.53 ± 7.87	131.67 ± 8.92

Fall in systolic blood pressure

In most patients in either group, the fall in SBP was within 20 mmHg (Table-**6**)

Table 6- Fall in systolic blood pressure

Fall in SBP (mmHg)	Group I	Group II
0-20	24 (80%)	23 (76.67%)
21-30	2 (6.67%)	6 (20%)
31-40	4 (13.3%)	1 (3.33%)

Change in mean Respiratory Rate

The mean respiratory rate was found to be highest at 1-4 hours postoperatively in Group I whereas in Group II, the maximum rise in mean respiratory rate was around 24-28 hours, post-operatively (Table **7**).

Table 7- Change in Mean Respiratory Rate

Mean respiratory rate	Group I (n=30)	Group II (n=30)
Preoperative	17.27 ± 2.16	17.8 ± 2.39
Intra-operative	18.13 ± 1.71	17.4 ± 2.33
Immediate postoperative	19.87 ± 3.18	18.3 ± 2.32
4 hrs post-op	**24.33 ± 3.46**	17.2 ± 2.08
8 hrs post-op	21.60 ± 5.76	17.47 ± 2.01
12 hrs post-op	17.4 ± 1.87	17.67 ± 1.86
16 hrs post-op	17.4 ± 2.00	18.67 ± 2.87
20 hrs post-op	17.33 ± 2.27	19.73 ± 3.64
24 hrs post-op	17.13 ± 2.17	20.4 ± 3.75
28 hrs post-op	17.90 ± 2.10	**21.33 ± 3.92**
32 hrs post-op	18.13 ± 2.36	21.27 ± 4.52
36 hrs post-op	18.0 ± 2.07	19.33 ± 2.61

Mean Duration of Analgesia

Table 8 shows the mean duration of analgesia along with the range of duration of analgesia. The difference in the duration of analgesia between Groups I and II was found to be statistically significant ($p< 0.001$).

Table 8- Mean Duration of Analgesia (hours ± S.D)

Group	Hours ± S.D	Range
I (n=30)	4.18 ± 1.01*	2.5 - 6.0 hrs
II ((n=30)	25.67 ± 5.40*	13 - 33hrs

Significance p<0.001*

Mean Pain Score

The mean pain score during the postoperative period was the highest at 5-8 hours for Group I. In Group II, it peaked at 29-32 hours (Table 9).

Table 9- Mean Pain Score (± S.D)

Postoperative period	Group I(n=30)	Group II(n=30)
0-4 hrs	6.76 ± 2.74	0
5-8hrs	9.54 ± 0.63	0
9-12hrs	--	0.22 ± 0.93
13-16hrs	--	1.02 ± 2.79
17-20hrs	--	1.59 ± 3.21
21-24hrs	--	2.20 ± 3.41
25-28hrs	--	4.76 ± 3.68
29-32hrs	--	8.45 ± 1.30
33-36hrs	--	10

Number of Patients requiring Analgesic Supplementation in the Postoperative Period

All patients in Group I had to be given analgesic supplementation by the end of 8 hours. Patients in Group II did not require supplementation till the end of 12 hours, but by the end of 36 hours all of them had asked for pain relief. The patients given supplementation were counted out of the study from that point onwards as far as duration of analgesia was concerned (Fig 1)

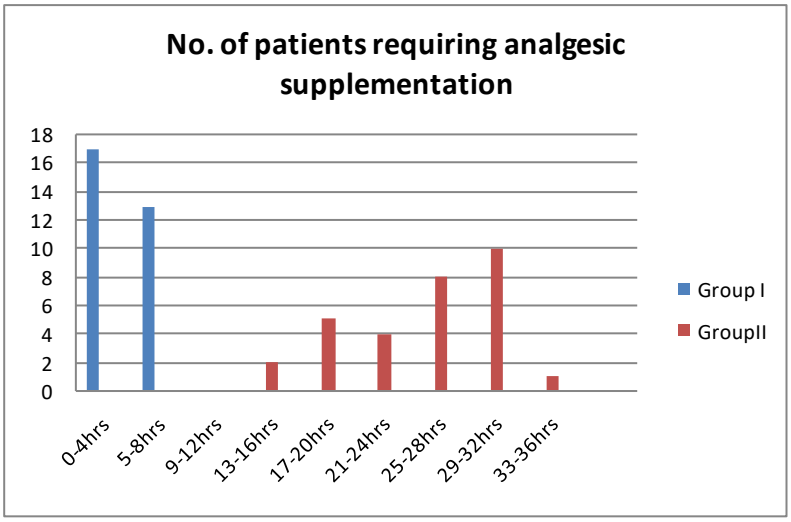

Figure 1: Number of Patients requiring Analgesic Supplementation in the Postoperative Period

Incidence of side effects

The incidence of sedation in Group II was significantly greater than in Group I ($p < 0.01$). Incidence of other side effects did not differ significantly (Fig 2).

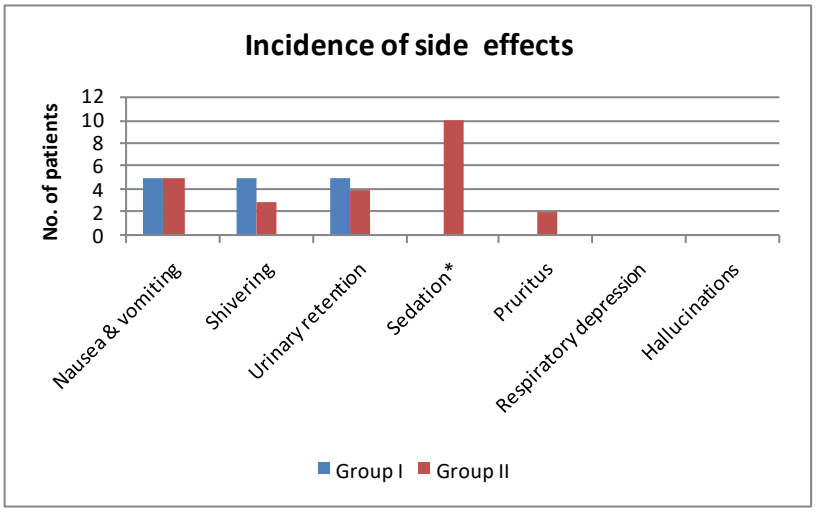

Fig 2: Incidence of side effects

DISCUSSION

The long duration of action and the analgesic efficacy of buprenorphine can be explained by its high lipid solubility and strong affinity for opiate receptors. High lipid solubility increases both, diffusion into

the spinal cord and the spinal concentration there, but because of the slow dissociation constant of the buprenorphine drug-receptor complex, removal from the spinal cord into the blood stream is very slow. [6,11] Also, the strong receptor affinity of buprenorphine allows pharmacologically effective occupancy of the receptor at small plasma concentrations. [12]

Duration and intensity of analgesia

The duration of pain relief with buprenorphine is substantially longer than with other narcotics. [13] In the literature, epidural doses of buprenorphine vary between 0.06mg and 0.3mg. [14, 15] The occasional need for very high intravenous doses to produce freedom from pain, plus the fact that for buprenorphine, the effective intravenous and epidural doses are supposed to be roughly similar, have not encouraged the giving of epidural single injection of more than 0.3mg. [16] There are very few comparisons of different doses in the same study. One group of investigators found a markedly intensified postoperative analgesia with an increase from 0.15mg to 0.3mg. [14] Analgesia from 0.1mg by the same authors in a pilot study was disappointing. [17]

Large inter-patient variation and failure rates of 10-20% are mentioned in most reports concerning postoperative analgesia with epidural opioids. [15] A good quality of analgesia with relatively low dose was originally considered one of the main advantages with this method of administering opioids, and high failure rates and dubious analgesia may be the result of inadequate dosage. In this connection, it is especially important to observe the variability in the ratio between the commonly recommended intravenous and epidural doses for a given opioid. There are very few studies in which buprenorphine was administered epidurally in doses depending on body weight. Miwa et al found that 4µg/kg or 8µg/kg of epidural buprenorphine provided postoperative analgesia that was no less than that of morphine (80µg/kg). [18]

In the present study, buprenorphine, 3µg/kg, in patients having body weight of 36-66 kg (i.e. buprenorphine dose varying from 0.11-0.2mg) provided good intensity and duration of analgesia, with a mean duration of 25.67 hours as compared to 4.18 hours of analgesia provided by the local anaesthetic group. Not only was the duration of post-operative analgesia significantly longer than the local anaesthetic group ($p<0.001$), the intensity of pain relief was also significantly better. The mean pain scores peaked around 29-32 hours and patients reported satisfactory pain relief.

An explanation for the prolonged duration of analgesia with buprenorphine is that the epidural space is highly vascularised, and the high lipid solubility of buprenorphine facilitates its passage into the systemic circulation. [19] As is the case with other opioids, the plasma concentration of buprenorphine will be so high as to contribute considerably to the analgesia. [19] The systemic effect may offset the reduced analgesia at the spinal level. Another explanation for the long duration with epidural buprenorphine may be that the more lipophilic drugs like buprenorphine form a depot of drug in the extracellular fat. This could provide a means for continued transfer of drug at low levels across the dura.

Side effects

The most common side effect observed in this study was sedation, followed by nausea and vomiting. The incidence of sedation was found to be 33.3%, which is significantly higher than the control group. The sedative effect of narcotics is said to be one of their desirable features in the treatment of postoperative pain. [20] In this study the duration of sedation was variable, but was never a cause for concern. On the contrary, the 'relaxed' feeling was welcomed by most patients.

Nausea and vomiting have been observed following epidural administration of all currently employed opioids. The incidence of nausea in postoperative

patients is usually around 30%, but it is dependent on many factors such as age, sex, type of operation, etc. Pain itself can elicit nausea and vomiting. Bromage et al [21] observed nausea and vomiting in 50% of subjects approximately 6 hours after epidural morphine, which coincided with its rostral spread. Gundersen et al [16] reported nausea and vomiting in 21 out of 45 patients treated with epidural buprenorphine. Compared to the above studies, the incidence of nausea and vomiting was lower in this study with an average of 16.67%. Lack of rostral spread of this highly lipophilic drug could be the explanatory factor, along with the fact that the high incidence of sedation resulted in less ambulation of the postoperative patients than would be normally expected. The nausea and vomiting responded well to parenteral anti-emetics.

Opioid analgesics cause an increase in urinary sphincter pressure and a decrease in control inhibition of detrusor tone. The influence of opioids on the autonomic control of the bladder function may be mediated through the opioid receptors within the spinal cord (Murray, 1984). Rawal et al reported an incidence of 22% urinary retention in 90 patients receiving epidural morphine. [22] In the present study, catheterization was required in 13.3% of the cases. The difference in incidence from the local anaesthetic group was not found to be significant.

Pruritus occurred in 2 patients in the whole study. Both complained of facial pruritus. Facial pruritus following extradural opioids is attributed variously to histamine release, an effect of opioid spreading to the medulla or the fourth ventricle, or opioid action in the substantia gelatinosa of the spinal cord, referring pruritus to distant site by neuronal transmission.

In one study, pruritus was present in 28% of the postoperative patients receiving epidural morphine 10mg, [14] but in only 1% of patients in studies of morphine 5mg [4] and 2mg [23] respectively. However, the incidence of pruritus that troubles the patient appears to be close to 1%. [4] In the present study, pruritus was mild and responded well to antihistaminics. It has been reported that prior use of local anaesthetic reduces the incidence of pruritus with epidural opioids. [24] This could be the reason for low incidence of pruritus, as buprenorphine was mixed with local anaesthetic before administration.

Hallucinations did not occur in any patient in the study, though it has been reported. [25] Respiratory depression was also found to be absent in the entire study. A respiratory rate of less than 14 per minute was not observed in any patient. Late onset respiratory depression has not yet been reported for buprenorphine. [20] This is not surprising because theoretically, highly lipophilic drug will soon be cleared from the water phase of the cerebrospinal fluid and will thus not reach the bulbar centres with the bulk flow of the CSF. Moreover, the distribution volume of a lipophilic drug will be larger than for a more hydrophilic drug. This explains the absence of respiratory depression with epidural buprenorphine.

SUMMARY AND CONCLUSION

The present study was undertaken to demonstrate the safety and efficacy of epidural buprenorphine for postoperative pain relief. A total of 60 patients were selected for the study and were divided into two groups of 30 patients each. Epidural buprenorphine, 3µg/kg body weight, along with local anaesthetics or local anaesthetic alone was administered to each of these groups respectively.

Buprenorphine administered alone into the epidural space failed to provide adequate operative analgesia in 10 patients and they all had to be supplemented with general anaesthesia.

The mean duration of analgesia in the local anaesthetic group was found to be 4.18 hrs. Most patients had to be given supplemental analgesia by the end of 4hrs and all by the end of 8 hrs. When buprenorphine was administered with local anaesthetics, the mean duration of analgesia

was 25.67 hrs. There was a significant increase in the duration of analgesia ($p<0.001$). The mean pain scores also improved and peaked around 29-32 hrs postoperatively. The intensity of analgesia was also better when buprenorphine was administered along with local anaesthetics.

The most common side effects observed were sedation and nausea and vomiting. While the degree of sedation which occurred was welcome, nausea and vomiting responded very well to anti-emetics. Catheterization of the urinary bladder was required in 13.3% of the cases. Other side effects found in this study were minimal. Respiratory depression did not occur.

The search for the ideal drug to be used epidurally for relief of postoperative pain continues. Buprenorphine is not a controlled drug due to minimum addiction potential is marketed preservative-free and provides a long duration of postoperative analgesia with minimum side effects. Thus, it may be concluded that it is closest to an ideal epidural opiate for postoperative pain relief.

The author humbly suggests that if the use of epidural buprenorphine is encouraged and popularized for postoperative analgesia after major surgery, then repeated parenteral injections of opiates could be safely avoided for up to 24 hrs or more. Besides, the advantages of early mobilization will protect the patient from many untoward postoperative complications.

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