

# Can intraperitoneal bupivacaine decreases pain in patients undergoing laparoscopic live donor nephrectomy? A randomized control trial

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## Abstract

**Purpose** To evaluate effect of intraperitoneal bupivacaine on postoperative pain in patients undergoing laparoscopic live donor nephrectomy.

**Methods** Hundred patients undergoing laparoscopic live donor nephrectomy were included in the study and were divided randomly into two groups based on computer-generated randomization chart of fifty each. Patients were made familiar with VAS chart preoperatively. Group A received 20 mL of 0.5 % bupivacaine, while group B patients received 20 mL of 0.9 % normal saline intraperitoneally. Postoperatively, patients were assessed based on VAS and requirement of rescue analgesic, hemodynamic parameters and presence of any adverse effects. Student's t test was used for statistical analysis.

**Results** At all-time interval, mean pain scores were higher in group B than group A. The difference between the mean

pain scores was statistically significant ( $p < 0.05$ ) at 0, 2 and 4 h. The mean dose of rescue analgesia (pentazocin, 30 mg in one vial) in group A was  $33 \pm 26$  mg which was significantly less as compared to group B where it was  $62 \pm 28$  mg. There was statistically insignificant difference between all cardiorespiratory factories at all-time intervals except for heart rate and mean blood pressure at 0 h in group A as compared to group B.

**Conclusions** Intraperitoneal bupivacaine is a simple, safe, inexpensive method for control of postoperative pain in patients undergoing laparoscopic live donor nephrectomy. Use of the correct dose and concentration of the drug are essential for effective pain control.

**Keywords** Laparoscopic live donor nephrectomy · Intraperitoneal · Bupivacaine · Local anesthetic

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## Introduction

Renal transplantation is the treatment of choice for the patients with end-stage renal disease [1]. Subjecting the donor to an open procedure not only increases donor's morbidity in terms of increased hospital stay and large painful scar, but also discouraged potential donors. This has motivated the surgeons to come up with a less morbid technical alternative, the laparoscopic donor nephrectomy and better pain control measures. Laparoscopic live donor nephrectomy (LLDN) is now the gold standard and preferred method for kidney harvestation in renal transplant surgery.

Postoperative pain is the main cause of delay in resumption of normal daily activity after any operative procedure. Despite better understanding of pain pathophysiology, pharmacology of analgesics and development of newer more effective analgesic techniques, many patients still

continue to experience considerable discomfort [2]. Pain after the Laparoscopic live donor nephrectomy is multifactorial in origin. Main sources of pain are port-site pain, low abdominal incisions (to retrieve the kidney), pelvic organ nociception, diaphragmatic irritation (shoulder tip discomfort from residual pneumoperitoneum) and urinary catheter discomfort. Inadequately treated postoperative pain may lead to chronic pain [3–6]. As one of the sources of pain is peritoneal, advocates that analgesia delivered locally to the peritoneal cavity may be of value in controlling pain postoperatively [7].

LLDN is performed on healthy non-diseased donors so it is even more important to keep the morbidity and mortality of live donors as low as possible and at the same time to harvest the kidney in optimal condition for transplantation [4]. Thus, recovery from a surgery which is done to benefit another human being should be early and pain-free as far as possible. The cornerstone of early recovery is better pain control in postoperative period. In order to achieve this, the present study was undertaken to assess the efficacy of intraperitoneal instillation of bupivacaine in alleviating postoperative pain following laparoscopic live donor nephrectomy.

## Materials and methods

For study purpose, a total of hundred and twenty-nine consecutive patients were screened. Out of which twenty-nine were excluded due to various reasons (Uncooperative and unwilling patients, those with history of anaphylaxis to local anesthetics or previous abdominal surgery) based on our exclusion criterion. After informed consent and approval from ethical committee, these patients were scheduled for laparoscopic donor nephrectomy under a standardized general anesthesia technique.

Induction of anesthesia was achieved with propofol 1 % (2 mg/Kg) IV slowly along with injection fentanyl 1.5 µg/kg IV after preoxygenation with 100 % oxygen for 3 min. This was followed by intubation with an appropriate sized endotracheal cuffed tube, i.e., facilitated by neuromuscular blocker vecuronium 0.5 mg/kg IV.

Anesthesia was maintained using controlled ventilation (Bain's circuit) with isoflurane (0.5–1.5 %) and nitrous oxide (N<sub>2</sub>O) 66 % + oxygen (O<sub>2</sub>) 33 %. Neuromuscular blockade was achieved with atracurium besylate. Patients were randomly allocated (using computer-generated random numbers) to one of the two groups in a double-blind manner. Patients with Group A labeled syringe (Study group) received 20 mL of 0.5 % bupivacaine (BC) intraperitoneally, while patients with Group B coded syringe (Control group) received 20 mL of 0.9 % intraperitoneal normal saline (NS). In both groups, 10 mL of the drug was

instilled onto renal bed, 5 mL onto Hepatodiaphragmatic area and 5 mL onto space between diaphragm and spleen after completion of nephrectomy and just before removal of trocars under direct vision by the surgeon who was unaware of the nature of the study drug. At the end of each procedure, residual pneumoperitoneum was evacuated manually. Surgical wounds were not infiltrated with local anesthetic solution. Postoperatively, patient was extubated and shifted to recovery room where following observations were recorded and analyzed.

- Postoperative pain scores at 0, 2, 4, 8, 16 and 24 h.
- Time to first analgesia and cumulative 24-h analgesic consumption.
- Postoperative hospital course (monitoring of heart rate, blood pressure (BP), respiratory rate (RR), SPO<sub>2</sub> and temperature at 0, 4, 8, 16 and 24 h).
- Incidence of adverse effect (nausea, vomiting, shoulder pain, sedation, shivering, CNS and CVS) at 0, 4, 8, 16, 24 h.

Surgeon and the anesthesiologist in the recovery room were unaware of the treatment to which each patient was randomized. Pain intensity was measured by visual analogue scale (VAS) [8]. Patient showing a VAS  $\geq 3$  or patients who request for analgesia were administered a supplemental dose of an analgesic (Inj. Pentazocine brand name Fortwin, 30 mg intravenous route). Results were reported as mean  $\pm$  SD. The sample size has been calculated on the basis of a study [9] where mean pain score of the normal saline (3.9  $\pm$  2.7) has been consulted. The sample size per group with level of significance as 5 % was calculated to be 50. At 0 min, a 20 % reduction in pain was presumed to be significant reduction. This sample size maintained at least 89 % power of the study. Data were collected and analyzed using Student's *t* test. SPSS (statistical presenting system software) for windows (version 15) software was employed for data analysis.  $p < 0.05$  was taken as significant in the study.

## Results

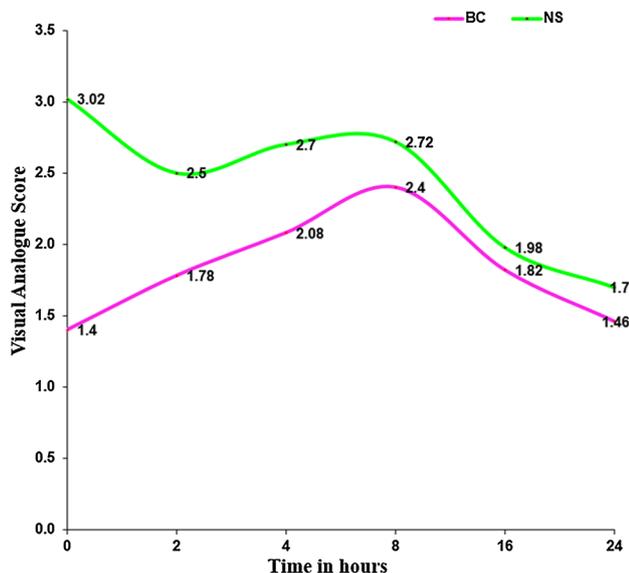
A total of 100 patients recruited for the study were comparable with regard to age, sex and body weight (Table 1). The mean intensity of postoperative pain was significantly lower in Group A than in Group B ( $p < 0.05$ ) at 0, 2 and 4 h postoperatively. Thereafter, it was statistically nonsignificant (Fig. 1). The maximum VAS seen in group A is at 8 h postoperatively (2.4  $\pm$  0.95) cm administration of rescue analgesic thereafter led to decrease in mean pain scores.

A number of patients requiring analgesia doses were significantly less, while mean time duration in postoperative

**Table 1** Table depicting patient demography comparison between bupivacaine (BC) (group A) and normal saline (NS) (group B), during LLDN

Parameter	Group A	Group B
Age (years)	48.52 ± 10.18	45.92 ± 08.79
Sex ratio (F:M)	36:14	36:14
Body weight (Kg)	66.60 ± 7.78	65.34 ± 6.77

Values are mean ± SD



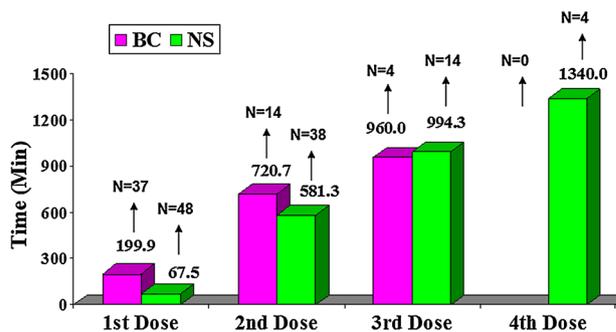
**Fig. 1** Trends in visual analogue score in group A (BC) versus in Group B (NS)

period for rescue analgesia was delayed significantly in group A as compared to group B. Thirteen patients in group A while only two patients in group B did not required any kind of rescue analgesia in postoperative period (Fig. 2).

The mean dose of rescue analgesia (pentazocin, 30 mg in one vial) in group A was 33 ± 26 mg as compared to group B where it was 62 ± 28 mg. The difference in mean dose of rescue analgesia in first 24 h was significantly less in group A than in group B (Table 2).

During our study, there was no significant difference for SPO<sub>2</sub>, respiratory rate and temperature between the two groups at any point of time. However, mean systolic blood pressure (Fig. 3) and mean heart rate were statistically lower in group A than in group B at 0 h. Mean operative time in group A was 110 ± 33 min and in group B was 117 ± 27 min (*p* > 0.05).

Though the incidence of adverse effects such as nausea, vomiting, itching, bradycardia, shoulder pain, hypotension and shivering was less in group A, but it did not achieved statistical significance. None of the patients were excluded



**Fig. 2** Trends in analgesic dose requirement in group A (BC) versus in Group B (NS); *n* = number of patient requiring analgesia

from the study because of uncontrolled pain or undesirable surgical outcomes such as conversion to open surgery or any serious cardiopulmonary adverse event.

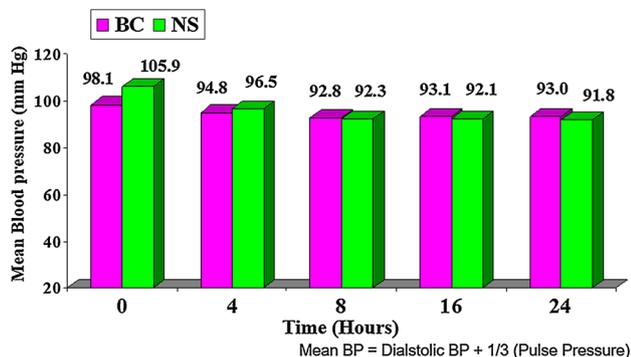
### Discussion

Despite LLDN now being the gold standard and preferred method for kidney harvestation in renal transplant surgery, still some patients in postoperative period experience considerable pain attributable to several components (parietal, visceral and shoulder pain) that have different intensities and different time courses [10]. It is imperative to state that as LLDN is done for a noble cause so whole procedure should be pain-free as far as possible. This will further encourage other donors to come and donate fearlessly. A number of methods have been tried to reduce postoperative pain after laparoscopic live donor nephrectomy such as use of nonsteroidal anti-inflammatory drugs, use of local anesthetic intraperitoneally, OPIOIDs analgesia, neuroaxial blocks and intravenous morphine infusion pumps for patient-controlled analgesia [11]. Couple of authors have conducted studies on intraperitoneal administration of local anesthetics during laparoscopic live donor nephrectomy as one of the modalities for relief of postoperative pain. However, scant studies were available to know analgesic efficacy of intraperitoneal bupivacaine as a single agent for postoperative pain relief after laparoscopic live donor nephrectomy [11, 12]. Thus, the present study was done to assess the efficacy of intraperitoneal instillation of bupivacaine in alleviating postoperative pain following laparoscopic live donor nephrectomy.

Bupivacaine has been used in a 0.5 % concentration in our study. This is based on its proven efficacy in studies done by various authors in different laparoscopic surgeries. Though we did not measure the plasma concentration of bupivacaine, several studies have shown that mean plasma levels are well below toxic concentration of 3 µg/mL when

**Table 2** Mean amount of rescue analgesia given in first 24 h

	Group A	Group B
Total number of patients	50	50
Number of patients requiring analgesia	37	48
Total dose of rescue analgesic in mg	33 ± 26	62 ± 28
<i>p</i> value	0.0001 (significant)	

**Fig. 3** Trends in mean blood pressure in group A (BC) versus in Group B (NS)

bupivacaine is administered in plain form in 100–150 mg (20–30 mL) dose [13–15]. The dose of drug used in our study is well below than those thought to cause systemic toxicity.

The number of females outnumbered the number of males in both the groups. This can be explained by the fact that most of the live donors seen in India are females (about 80 %) [16]. Lower postoperatively VAS in group A during early postoperative period, i.e., at 0, 2 and 4 h can be attributed to better control of pain due to the effect of local anesthetic given intraperitoneally. Therefore, the requirement of first dose of analgesia was delayed in group A in comparison with control group (group B). Our results correlate well with the observation made by Golubović et al. [17] in laparoscopic cholecystectomy and Marks et al. [5] in laparoscopic gynecological procedures, in which they demonstrated that intraperitoneal bupivacaine is effective as analgesic in early postoperative period (2 vs. 6 h, respectively).

However, our study does not correlate with the study done by Rademaker et al. [18] who did not find any significant difference in VAS between the control (0.9 % 20 mL NaCl,  $n = 15$ ) and treatment group (0.25 % 20 mL bupivacaine,  $n = 15$ ). Small sample size and low concentration of bupivacaine can be a cause of lack of efficacy of drug in this study.

In our study, the number of patients requiring rescue analgesia was 37 in group A versus 48 in group B. Mean time to first analgesia is 199.9 min in group A

versus 67.5 min in group B. Total dose of rescue analgesic required in first 24 h was also significantly less in group A (33 ± 26 mg of pentazocine) versus group B (62 ± 28 mg of pentazocine). This observation implies better analgesic effect of intraperitoneal bupivacaine as compared to normal saline.

Delayed requirement of rescue analgesic in first 4 h in study group could be explained by the fact that after intraperitoneal administration of bupivacaine, it gets absorbed into systemic circulation and duration of action of parentally administered drug being around 3–6 h [13, 14]. Initially, the high mean requirement of rescue analgesic in group B could be explained by the fact that being a control group, the patients had more pain in immediate postoperative period so a need for higher mean rescue analgesic requirement. Thus, correlating with study done by Sulekha et al. [19] in which authors demonstrate statistically significant reduction in frequency of dosing and reduction in mean requirement of analgesic in treatment group in patients undergoing laparoscopic cholecystectomy.

In our study, there is no significant difference in mean heart rate, SPO<sub>2</sub>, temperature and respiratory rate in two groups at any time. However, mean blood pressure and heart rate were significantly less at 0 h in group A which may be attributed to the fact that better control of pain and analgesia in immediate postoperative period in these patients. The results were similar to the study done by Pasqualucci et al. [20] who studied effect of intraperitoneal bupivacaine on hemodynamic parameters. He concluded that heart rate, blood pressure and respiratory rate which are indicators of patient discomfort showed significant decrease in treatment group as compared to control group.

Longer mean operative time may also increase postoperative pain in laparoscopic surgery. This factor was not significant in our study as the two groups were comparable with regard to mean operative time. Similarly, residual pneumoperitoneum may also aggravate postoperative pain intensity so to nullify this effect manual evacuation of residual CO<sub>2</sub> gas was done at the end of procedure in each case.

Incidence of emetic symptoms (nausea, vomiting) as well as incidence of shoulder pain was less in group A when compared to group B can be explained by the fact that postoperative pain was controlled better in group A as compared to group B. Moreover, due to local analgesic effect of bupivacaine when instilled in subdiaphragmatic space decreases incidence of referred shoulder pain.

One of the limitations of the study is failure to quantify pain objectively rather than subjectively using VAS system. In our study, we have instilled bupivacaine just before removal of trocars, while some studies advocate to instill local anesthetics both before the start of operation, i.e., after creating pneumoperitoneum and before removal of

trocars [21] which might have better analgesic effect of the drug. Moreover, there are further different predictive factors for postoperative pain such as pneumoperitoneum pressure during laparoscopy, type and length of organ retrieval incision and nearness of subcostal laparoscopic port with respect to ribs; exploring these factors could be the goal of future studies.

## Conclusion

Intraperitoneal bupivacaine significantly reduces pain scores in early postoperative period without significantly increasing incidence of adverse effect or hemodynamic complications. It is a simple, safe, inexpensive method for control of postoperative pain in patients undergoing laparoscopic live donor nephrectomy. Use of the correct dose and concentration of the drug are essential for effective pain control.

**Author's contribution** Ganpule A was involved in manuscript writing, data analysis and proof reading; Jairath A was involved in project development, manuscript writing, data collection and analysis; Gupta S, Mishra S, Sabnis RB and Desai MR were involved in manuscript editing and proof reading.

## Compliance with ethical standards

**Conflict of interest** None.

**Ethical approval** All procedures in this study were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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