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Outcome of Transperitoneal Laparoscopic Nephrectomy Using Multimodal Analgesia in Terms of Postoperative Pain Control and Recovery: A Randomised Double Blind Control Trial

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Abstract: Transperitoneal laparoscopic nephrectomy (TLN) is presently the gold standard approach for both simple and radical nephrectomy. Though minimally invasive, TLN patients experience significant postoperative pain. We tried to evaluate the role of multimodal analgesia on postoperative pain control and recovery, both in terms of efficacy and safety. Forty patients of transperitoneal laparoscopic nephrectomy (both benign and malignant pathology), aged between 30-75 years; of both sex; ASA I-III; were randomly allocated in two groups. Group-P (n=21) received 100 mL of Paracetamol IV over 10 min, 15 min before induction, Group-**C** (n=19) received 100 ml normal saline instead of paracetamol. Protocol of induction and maintenance of anesthesia was same in both the groups. At the end of surgery both groups received port site infiltration block with 25 ml of 0.5% levobupivacaine. Post-operative pain and sedation were assessed at 10 mints, 30 mints, 45mints, 1hr, 2hr, 4hr, 6hr, 8hr, 12hr, 24 hr and 48 hours with VAS scores/sedation score. Fentanyl 1 µg/kg was used as rescue analgesic when VAS > 4. Data of intra-operative variables, postoperative pain relief, rescue analgesics requirement, and patient satisfaction were compared. VAS scores were similar in both the groups during first four postoperative hours, but at 8^{th}, 12^{th}, 24^{th} and 48^{th}postoperative hour VAS score in Group-C was significantly higher ($p<0.05$). 1^{st} rescue analgesic requirement was delayed in Group-p compared to group-C (287±18.3 vs244±12.6) and the total postoperative 24hrs fentanyl consumption was also found to be lower in Group P (120 ±45.91 vs 250 ±70.34) ($p<0.05$). Group-P had shorter SICU and hospital stay. Group-P showed higher patient satisfaction also. Intravenous paracetamol infusion and levobupivacaine wound site infiltration as part of multimodal analgesia effectively control post-operative pain after transperitonial laparoscopic nephrectomy.It also reduces postoperative fentanyl consumption and provide excellent patient satisfaction with no added side effects.

Keywords: Laparoscopic nephrectomy, Multimodal analgesia, intravenous paracetamol, levobupivacaine infiltration.

INTRODUCTION

Effective pain control in the postoperative period increases patient satisfaction, improves sleep, results in a more rapid recovery and shorter hospital stay, decreases total cost of treatment and lowers the risks of postoperative complications, such as development of deep vein thrombosis and pulmonary complications [1]. There are many different drugs like opioids, NSAIDS, local anaesthetic agents that can be used to treat postoperative pain through different routes; each having its own risk of adverse effects and complications [2]. Complex nature of post laparoscopic pain needs multimodal analgesia for effective pain control. Paracetamol, although previously used mainly as an antipyretic, is increasingly being used as an analgesic and it's infusion has been found to be safe and can be given in single or multiple doses in major surgeries [3]. On the other hand, opioid analgesics are increasingly taking the role of "rescue analgesics" for acute pain after laparoscopic surgery. Local anaesthetic infiltration of the wound site is also being increasingly used as an adjunctive measure. So, use of multimodal

analgesia is rapidly becoming the standard of care for preventing pain after laparoscopic procedures at most surgical centres throughout the world [4-6].

Acetaminophen (paracetamol or N-acetyl- P-aminophenol) produces a central analgesic effect, its precise mechanism(s) remain unknown. Postulated targets include cyclo-oxygenase isoenzymes, endogenous opioid or serotoninergic bulbospinal pathways, and/or cannabinoid/ vanilloid tone [7]. Paracetamol also act as a TRPV-1 agonist and inhibits prostaglandin within the hypothalamus [8, 9].

Levobupivacaine is an amino-amide local anaesthetic drug belonging to the family of n-alkyl substituted pipecoloxylidide. It is the S-enantiomer of bupivacaine and 13 per cent less potent than racemic bupivacaine[10]. The drug binds to the intracellular portion of sodium channels and blocks sodium influx into nerve cells, which prevents depolarization [11]. Levobupivacaine appears to cause less myocardial depression than both bupivacaine and ropivacaine, despite being in higher concentrations [12].

MATERIALS AND METHOD

This randomized controlled study was conducted in the department of Urology, NRS medical College, Kolkata between August 2011 to April 2014, on 43 patients who underwent trans-peritoneal laparoscopic nephrectomy. The research protocol was approved by the institute ethics committee, and all the patients provided written informed consent for the study.

The inclusion criteria were all patients, aged between 25-65 yrs, of either sex, ASA I-III, who was planned for laparoscopic Trans-peritoneal nephrectomy for non-functioning kidney or renal malignancy (stageT1/T2). The exclusion criteria included procedures with conversion to open nephrectomy. Patients having contraindications to paracetamol (hypersensitivity, liver dysfunction, severe renal disease)or to nonsteroidal anti-inflammatory drugs (NSAIDs) (esophago-gastroduodenal disease, renal insufficiency andabnormal coagulation), any contraindication for levobupivacaine (sepsis, renal failure, cardio-respiratory insufficiency) or patients who are on steroids/ opioids before surgery, morbid obesity, neuro-psychiatric diseases were also excluded.

Patients were randomly allocated in two groups by a computer-generated list. Group-P (IV Paracetamol group) received 100 mL of Paracetamol IV (Perfalgan1 gm) over 10 min; Group-C (Control group) received 100 ml normal saline, 15 min before induction. Of the 43 patients initially enrolled, 3 patients were finally excluded from the study; one radical nephrectomy patient was converted to open surgery because of intra-operative bleeding, two simple nephrectomies ware converted to open surgery because of non-progression. At the end of the study, 19 patients in the control group (Group C) and 21 patients in the Paracetamol infusion group (Group P) were analysed.

As a standard protocol all the patients underwent trans-peritoneal laparoscopic nephrectomy in the lateral decubitus position, with the operative table flexed optimally to open the space between the lowest rib and the iliac fossa. A 15-mm Hg carbon dioxide pneumoperitoneum was established using the 12-mm Optiview direct laparoscopic access technique, at the lateral border of ipsilateral rectus muscle slightly cranial to the level of the umbilicus.

Two additional ports, one 5 mm and one 12 mm were placed under direct vision in the epigastrium and hypogastrium region. An additional 5-mm port was used at the sub xiphoid region/flank to retract the liver/spleen. After completion of the laparoscopic nephrectomy the specimen was entrapped in an indigenous specimen retrieval bag made from a Urobag and is retrieved through a transverse Pfannenstiel skin incision made above the symphysis pubis. The extraction incision is then closed in 2 layers with 1-0 vicryl. 10-12-mm trocar incisions are closed under direct vision with absorbable sutures. The 5-mm ports are closed only at the skin level.

Anesthesia management

On entering operation room standard monitor (Phillips inteliview MP 30) was attached & crystalloid infusion started through 18G i.v.cannula. Group-P(IV Paracetamol group) received 100 mL of Paracetamol IV (Perfalgan1 gm) over 10 min, Group-C (Control group) received 100 ml normal saline, 15 min before induction. After 3 min of pre oxygenation with 10 L / min flow, patients were induced with etomidate 0.3 mg/kg slow IV over 30-60 seconds, fentanyl (2 µg/ kg), and atracurium (0.5 mg/kg).Anesthesia was maintained by 1–2% sevoflurane in nitrous oxide and oxygen (ratio 2:1) and fentanyl infusion @ 0.5 µg/kg/min, atracuriuminfution @5-10µ/kg/min. The lungs were mechanically ventilated to maintain EtCO2 between 28–34 mm Hg depending on the different stages of laparoscopy. BIS was maintained between 40-60. At the end of the surgery port site/ specimen retrieval site infiltration was done with 25 ml of 0.5% levobupivacaine (two 10mm port and two 5mm port-3ml each, specimen retrieval site -13ml). Approximately 30 min before end of surgery infusion of atracurium and fentanyl were stopped. Post-extubation all patients were transferred to SICU for monitoring.

Operative data including indication for nephrectomy, total operating time, extraction time, estimated blood loss (EBL), specimen weight and size (maximum diameter), incision length were recorded. Postoperatively pain score, time to unassisted ambulation, complication (if any) and length of hospital stay was assessed.

Postoperative pain was assessed using a visual analog scale (10 cm VAS scale; 0 - "no pain" and 10 - "worst pain imaginable"). Postoperative analgesia was provided to all patients with IV fentanyl 1 µg/kg as "rescue analgesic" only when the VAS score exceeded 4.

The degree of sedation was determined according to a sedation score ranging from 0 to 2 (0- alert, 1- drowsy but arousable to voice, and 2- very drowsy, but arousable to shaking). Post operation VAS scores and sedation scores were assessed at 10 mints, 30 mints, 45mints, 1hr, 2hr, 4hr, 6hr, 8hr, 12hr, 24 hr and 48 hr after surgery. Total fentanyl consumption at these times for both the groups was also recorded. If nausea and/ or vomiting occurred, the same was noted and iv 4 mg ondansetron was given. All measurements were recorded by a resident who was blinded regarding the study group. At the end of the study, the patients were questioned about their remarks and impressions on postoperative pain or other problems. They were requested to evaluate their satisfaction from the point of patient comfort as poor=0, fair=1, good=2, excellent=3 and the results were recorded.

STATISTICAL ANALYSIS

Data were collected in computer generated sheet. Statistical analysis was performed by Statistical Packet for Social Sciences (SPSS, Chicago, Il, USA) version 18.0 for Windows. The data were analysed and compared using the repeated measure variance analysis, one-way ANOVA test, chi-square test and Fisher's exact test. Fisher's exact t-test and chi-square test was used to analysenominal data; $P<0.05$ was considered to be significant.

RESULTS AND ANALYSIS

Forty three adult patients were initially enrolled in the study. Both the groups were demographically similar in terms of age, sex, height and BMI (Table-1). Three patients were finally excluded from the study; one radical nephrectomy patient was converted to open surgery because of intra-operative bleeding, two simple nephrectomies ware converted to open surgery because of non-progression. At the end of the study, 19 patients in the control group (Group C) and 21 patients in the Paracetamol infusion group (Group P) were analysed.

Operative variables like duration of surgery (126.73±19.41 vs 134.44±15.93), intra operative blood loss (249 ± 60 ml vs 273±45 ml), number of ports (4 in all cases), length of incision (10.7 ±2.6) vs 10.9±2.4), were statistically not different in both the groups (Table-1).

Table-1: Table showing patients demographics and surgical parameters

Parameters		Control (n=19)	Paracetamol (n=21)
Age (in year) (Mean±SD)		43.01±8.2544	41.42±9.3056
Sex	Male	52.63%	57.14%
	Female	47.37%	42.86%
Body weight(Mean±SD)		58.42±4.88	56.52±3.80
Height(Cm) (Mean±SD)		157.20 ± 5.48	159.22 ± 6.37
BMI		23.7 ± 2.58	22.5 ± 2.08
ASA	I	9	10
	II	6	7
	III	4	4
Duration of surgery in min (Mean±SD)		126.73±19.41	134.44±15.93
Intra-operative blood loss ml (Mean±SD)		249±60	273±45
Number of ports		4	4
Length of specimen retrieval wound (cm)		10.7(2.6)	10.9(2.4)

Immediate post-operative recovery parameters (Table-2) like spontaneous eye opening, extubation time and response to verbal command was earlier in the paracetamol group compared to the control group. Post-operative SICU stay (mints) was less in group-P.

Table-2: Table showing immediate post-operative recovery parameters and post-operative events

Parameters		Control	Paracetamol
Recovery Profile (post skin closure) minutes	Spontaneous eye opening	8.8±2.3	5.2±1.8
	Extubation time	10.06±1.3	7.1±1.03
	Response to verbal command	12.01±1.07	8.60±1.27
Post op SICU stay (min)		57.01±21.67	30.77±19.33
Sedation Score(>3)		2/19 (10.52%)	2/21(9.52%)
PONV(nausea)		3/19(15.78%)	2/21(9.52%)
Incidence of shoulder pain		1(5.26%)	1(4.76%)

Post-operative static and dynamic and pain score (VAS Score) were assessed in different point of time (Table-3). VAS score was significantly less (all < 4) in 10, 30, 45 min, 1hr and 4 hr in both the groups, indicating that in first four hours of post-operative period pain was well controlled in both the groups, no patients needed any rescue analgesia in this period. This may be because of the levobupivacaine infiltration of the wound. But after 4 hours till 48 hours, VAS score was significantly more in control group, both for static and dynamic pain (cough & movement), proving that pain control was better with IV paracetamol, even on ambulation.

Table-3: Dynamic and Static pain score (VAS SCORE) in different point of time

VAS score		Control Gr	Paracetamol Gr
VAS -10 MIN		2.7±0.4	2.1±0.4
VAS-30 MIN		2.9±0.6	2.1±0.3
VAS-45 MIN		2.9±0.4	2.2±0.7
VAS -1 HR		2.87±0.4	2.5±0.4
VAS-4 HR		3.3±0.4	3.0±0.5
VAS-8 HR	rest	5.5±0.3*	3.3±0.6
	cough	7.08±0.3	5.25±0.3
VAS-12 HR	rest	4.7±0.3*	3.3±0.3
	cough	7.08±0.3	5.25±0.3
	movement	8.31±0.7	5.67±0.3
VAS-24HR	rest	4.9±0.3	3.4±0.3
	cough	6.98±0.4	4.8±0.4
	movement	7.03±0.9	5.25±0.5
VAS-48 HR	rest	4.4±0.7*	3.3±0.7
	cough	5.88±0.4	3.54±0.4
	movement	6.02±0.9	3.84±0.5

Analysis of the need of rescue analgesia showed (Table-4) that requirements of 1st rescue analgesic were earlier in control group (242±12.6 vs 287±18.3). Total requirement of rescue analgesic, fentanyl were also more in group-C (250 ±70.34 vs 120 ±45.91). Because of good pain control the patients in the paracetamol group could be made ambulatory comparatively earlier (13.5±3.2 vs 18.3±2.6).

Table-4: Table showing comparison of two groups in terms first rescue analgesia time, total fentanyl consumption, ambulation time and hospital stay

Parameters	Control	Paracetamol
1ST rescue analgesic*time(mints)when VAS>4	244±12.6	287±18.3
24 hrs total fentanyl* consumption(µg)	250 ±70.34	120 ±45.91
Ambulation (hours)	18.3±2.6	13.5±3.2
Length of hospital stay (days)	3.39	2.83

Post-operative complications in terms of PONV, sedation and shoulder pain were similar in both the groups showing that IV paracetamol infusion did not increase any complication/ side effects in the post op patients. Post-operative hospital stays (in days) also less in group-P (3.2±1.3 vs 5.11±0.9). Because of better postoperative pain control, early ambulation, no significant complication and early discharge from hospital, most of the patients who received IV paracetamol had an "excellent" satisfaction score (Table-5).

Table-5: Patients Satisfaction According to Study Groups

	Group-C(n=19)	Group-P(n=21)
Excellent	68.42%	77.19%
Good	19.23%	18.36%
Fair	12.35%	4.45%
Poor	-	-

DISCUSSION

Pain is probably the most distressing experience for the patient in the post-operative period. Warfield and colleagues noted incidence of post-

operative pain in 77% patients, among them 80% individuals experiencing moderate to severe pain [13]. Poor postoperative pain control leads to longer time to ambulation [14], reduced activity causing atelectasis, pneumonia, deep vein thrombosis, pulmonary embolism. All these events ultimately lead to longer hospital stay (LOS), psychological trauma, and decreased patient satisfaction [15, 16]. Poorly managed post op pain also leads to a higher prevalence of chronic pain syndromes as long term effect [14, 16, 17].

Opiods and NSAIDS are the two most commonly used agents used in postoperative pain management. Opioids are highly effective in the management of post-operative pain but its use is decreasing gradually due to high incidence of side effects (e.g., respiratory depression, sedation, nausea and vomiting, constipation, urinary retention and illeus). Even therapeutic dose of opioids may cause respiratory depression and sedation, both of which increase the risk of aspiration, respiratory failure, decreased mobility and falls [18, 19]. All these unwanted events leads to significant patient discomfort, delayed recovery and prolonged hospital stay [2, 18]**.**

NSAIDS, although one of the most commonly used medication for control of post-operative pain, has its own complication, causing GI bleeding, gastric mucosal damage, and renal toxicity. These side effects limit their use in the postoperative setting particularly in renal compromised patients [2, 20]. NSAIDS use in patients of nephrectomy has to be more judicious because of its nephrotoxicity potential.

The complex nature of pain after laparoscopic procedures suggests that effective analgesic treatment should be multimodal [21, 22]. Multimodal analgesia uses administration of both opioids and non-opioids, which act differently through central and peripheral pathways and receptors. Multimodal analgesia optimizes analgesic efficacy using lower doses of each of the respective agents, thus limiting the dose related side effects, at the same time achieving good post operative pain control, improved recovery profile, reduced hospital stay, lower total cost of therapy, early return to daily life, effectively improving patients satisfaction [2, 20, 23-26].

Bisgaard *et al*., in their study concluded that a multimodal analgesic regimen consisting of a preoperative single dose of dexamethasone, incision site local anaesthetic infiltration (at the beginning and/or end of surgery), and continuous treatment with NSAIDs or COX-2 inhibitors during the first 3–4 postoperative days produced the best clinical outcome [27].

Studies also suggested that in combination with local anaesthetic infiltration, ketorolac (30 mg i.v. or injected with the local anesthetic) is highly effective and allowed patients to be discharged home at least 1 h earlier without producing hematoma, wound complications in the post discharge period [28].

Intra-abdominal administration of levobupivacaine rendered satisfactory analgesia in patients undergoing abdominal hysterectomy [29] and laparoscopic cholecystectomy.

The use of continuous local anaesthetic techniques (e.g., for perineural blocks or wound infiltration) has become increasingly popular due to their ability to control moderate-to-severe pain after major ambulatory orthopaedic surgery procedures [30-34].

A. A. Louizos used pre-incisional and intraperitoneal 0.25% levobupivacaine in laparoscopic cholecystectomy for postoperative analgesia .He found lower pain scores during rest, cough, and movement. Need of rescue analgesia was significantly lower with levobupivacaine (35% vs 84%). The incidence of right shoulder pain was significantly lower [35].

Local infiltration of levobupivacaine had been used in different surgical procedures namely off-pump CABG [36], laparoscopic cholecystectomy [35, 37], laparoscopic gynaecological surgery [38, 39], inguinal hernia repair [40]. All these studies showed that peri-incisional infiltration effectively reduces pain & analgesic requirements, minimize hospital stay, and enhance patient's satisfaction.

In November 2010, the FDA approved the use of intravenous paracetamol infusion (IVP) for the management of mild to moderate pain and for the management of moderate to severe pain with adjunctive opioid analgesics [41].

When paracetamol given by IV, it has a fast and reliable onset of analgesia, reaching a clinical analgesic effect within 5 minutes [42] and reaching therapeutic plasma concentrations in 15 minutes compared with the 45 minute onset of oral acetaminophen [43].

A number of studies showed statistically significant reduction in pain scores, opioids consumptions and increased patient satisfaction among the patients who received IVP compared to the patients who were in the control group [2, 41-50]. However, Brodner *et al*., could not find any difference among the groups in regard to satisfaction with their pain treatment postoperatively [47].

In one study with cholecystectomy in female patients, authors preoperatively administered oral oxycodone in one group (n=10) or 1gm oral paracetamol in another group (n=10). On evaluation of postoperative pain and side effects, they found similar postoperative pain scores and side effects, with no difference determined between the groups [51].

In another study by Hein *et al*., patients undergoing a minor gynaecological surgery, 8 mg of oral lornoxicamwas given to one group and 1000 mg of oral paracetamol was given to another group 60 min before induction. It was observed that VAS pain scores at postoperative 30and 60 min were similar in both the groups; however, the VAS score was higher in the control group (did not receive medicines) [52].

In our study, we used IVP (IV paracetamol) 1 gm as pre-emptive analgesic in transperitoneal laparoscopic nephrectomy. All patients received 0.5% levobupivacaine infiltration block at port sites/specimen retrieval sites. Intra-operative analgesia was maintained in both the groups by fentanyl infusion which was stopped 30 min before the end of surgery. We assessed IV paracetamol's effects on post-operative analgesic effectiveness, postoperative analgesic requirement in the form of opioids consumption as rescue analgesic, time to unassisted ambulation, frequency of side-effects, patients' satisfaction and hospital stay. Pain control was good for both the groups in first 4 hours of operation, no patient needed any rescue analgesia within this period. This is probably the effect of incision site levovobupivacaine. But after 4 hours is elapsed, pain is more in patients who did not receive paracetamol. This group needed rescue analgesics earlier and ultimately needed more dose of fentanyl. In these two demographically similar groups of patients with similar surgical parameters and identical measures of perioperative pain control, the only thing which made the difference was the pre-emptive use of IV paracetamol. So, IV paracetamol was an effective analgesic. IVP did not increase the incidence of nausea and vomiting, sedation which is a common side effect with opioids [52, 53].Patients satisfaction score was better in Group-P.

This is consistent with the findings of various previous studies where opioid-sparing effects of NSAIDS, COX-2 inhibitors, and intravenous paracetamol have beenfound to be in the range of 20–30% [54, 55]. IVP had been used in laparoscopic cholecystectomy [53, 56] & found to have a morphine reducing effect (31–37%) in 1st 24 hrs [57].

The unique feature of our study is: First: the nature of surgery with its degree of invasiveness and Second: effect of IV paracetamol on both static and dynamic pain. The previous studies were done in laparoscopic cholecystectomy [54], tonsillectomy [55], dental extraction [53] and minor gynaecological procedure. Laparoscopic trans-peritoneal nephrectomy is definitely a more invasive surgery than the previous surgeries in terms of more extensive intra-peritoneal dissection, prolonged duration of surgery and bigger incision sites. Even with this degree of invasiveness IV paracetamol was effective. We also studied "dynamic" pain relief along with "static" pain relief. Early ambulation is a goal of any minimally invasive surgery, effective control of dynamic pain postoperatively with IV paracetamol fulfils the basic aim of multimodal analgesia, reducing post op complication, ensuring early discharge from hospital and good patient satisfaction.

CONCLUSION

Intravenous paracetamol infusion along with levobupivacaine infiltration as part of multimodal analgesia effectively control post-operative pain after trans-peritoneal laparoscopic nephrectomy. It also reduces postoperative fentanyl consumption and provide excellent patient satisfaction with no side effects.

Conflict of Interests

The authors declare that they have no conflict of interests as pertains to the materials or methods specified in this study or the data presented in this paper.

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