Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i19.3721

A COMPARATIVE STUDY OF LEVOBUPIVACAINE AND LEVOBUPIVACAINE PLUS DEXMEDETOMIDINE IN CONTINUOUS EPIDURAL INFUSION FOR INTRA OPERATIVE ANALGESIA IN PATIENTS UNDERGOING OPEN RENAL TRANSPLANT SURGERIES

Dr. Kinjal Ashokbhai Vaghela[1], Dr. Viralkumar Ashokbhai Vaghela[2], Dr. Hetal Chaudhari[3], Dr. Dharmesh Galiya[4*]

[1]Senior Resident, Department of Anesthesia, GMERS Medical College and Hospital, Gandhinagar
[2]Senior Resident, Department of Anesthesia, GMERS Medical College and Hospital, Vadnagar
[3]Senior Resident, Department of Anesthesia, GMERS Medical College and Hospital, Gandhinagar
[4*]Consultant Radiologist, Department of Radiodiagnosis, SMVS Hospital, Gandhinagar

***Corresponding Author:** Dr. Dharmesh Galiya
Consultant Radiologist, Department of Radiodiagnosis, SMVS Hospital, Gandhinagar
Email: dharmeshgaliya@gmail.com

Received: 1-12-2023 **Revised:** 10-12-2023 **Accepted:**14-12-2023

Abstract

Background and aims: General anaesthesia with epidural anaesthesia is preffered technique for renal transplant surgery as it provides superior muscle relaxation and controlled diaphragmatic movement during surgery with added advantage of stable hemodynamics and better perioperative field. Dexmedetomidine, a selective alpha-2 agonist has been found to be a better epidural adjuvant with more stable cardio-respiratory parameters, higher sedation score and prolongs postoperative analgesia.

Method: Prospective, randomised, double blind study. It was conducted on 80 adult ASA III or IV patients of either sex, scheduled for elective renal transplant surgery requiring general and epidural anaesthesia (during 2018-2020). Group-L received epidural bolus dose of 0.25% L-bupivacaine(10ml) followed by infusion of 0.125% L-bupivacaine @0.1ml/kg/hr, Group-LD received epidural bolus dose of 0.25% L- bupivacaine plus dexmedetomidine 10mcg(10 ml) followed by infusion of 0.125% L-bupivacaine plus dexmedetomidine 40mcg(20ml) @0.1ml/kg/hr. In both the groups intraoperative hemodynamics, depth of anaesthesia, requirement of inhalational agents and muscle relaxants, duration of postoperative analgesia and requirement of rescue analgesia were compared.

Result: There is statistically significant difference was observed in hemodynamics intraoperative as well as postoperatively ($p<0.01$). Requirement of inhalational agent and muscle relaxants was significantly less in group-LD($p<0.01$). Duration of postoperative analgesia was prolonged and requirement of total no. of rescue analgesia were significantly less in group-LD($p<0.01$). Postoperative sedation (Ramsay sedation scale) was higher initially in group-LD.

Conclusion: Dexmedetomidine better adjuvant to L-bupivacaine as it has longer duration of analgesia, hemodynamic stability, muscle relaxant and inhalational agent sparing effect and better sedation.

Keywords: Epidural anaesthesia, L-bupivacaine, Dexmedetomidine

Introduction

Renal transplantation is most effective renal replacement therapy for patients with end stage renal diseases (ESRD). Important goals of perioperative management are to ensure stable intraoperative hemodynamics, provide optimal perfusion for the newly transplanted kidney and to provide good analgesia during perioperative period.

General anesthesia is preferred technique for renal transplant as GA is considered to provide superior muscle relaxation and controlled diaphragmatic motion during the surgery. Epidural anaesthesia along with general anesthesia can have added advantage to provide stable hemodynamics and better operative field. Epidural anesthesia reduces the surgical stress by blocking the nociceptive impulses from the operative site and reduces the blood loss, improve respiratory and bowel function and decreased incidence of deep vein thrombosis. Regional anesthesia techniques offers superior pain relief and early mobilization especially when local anaesthetic combined with adjuvants like alpha-2 agonists, opioids, non-opioids etc.

Levobupivacaine is an amide local anaesthetic similar to bupivacaine but with lesser cardiac and neurotoxicity adverse effects. Dexmedetomidine is a selective alpha-2 agonist. It is used as an adjuvant to local anaesthetic and has sedative, anxiolytic, analgesic and sympatholytic activity. Dexmedetomidine has been found to be a better epidural adjuvant with more stable cardio-respiratory parameters and higher sedation scores

Material and Methods

This was prospective, randomised, double blind study. After taking written informed consent from the patients and clearance from the institutional ethical committee, this study was conducted in IKDRC civil hospital Ahmedabad during 2019-2020. It was conducted on 80 adults ASA III or IV patients of either sex, scheduled for elective renal transplant surgery requiring general and epidural anaesthesia. 80 patients were divided randomly by the sealed envelope technique into two equal groups of 40 patients each. Group-L: Epidural bolus dose of 0.25% L-Bupivacaine(10ml) followed by epidural infusion of 0.125% L-bupivacaine(20ml)@ 0.1 ml/kg/hr. Group-LD: Epidural bolus dose of 0.25% L-bupivacaine plus Inj. Dexmedomidine 10 microgram(10ml) followed by epidural infusion of 0.125% L-bupivacaine plus Inj. Dexmedetomidine 40 microgram(20ml)@0.1ml/kg/hr. All the patients underwent pre-anaesthetic checkup, history of dialysis and clinical examination were done and relevant clinical investigations were noted. Pre-operative hemodialysis was advised for all patients on the day before surgery. Patients were kept NBM for 8hours for solid food. On the day of surgery, post- dialysis morning investigations like CBC, ECG, CXR, Coagulation profile, S. electrolyte were done. In the operating room, standard monitors were applied. Patients were pre-medicated with Inj.Ondansetron

0.1 mg/kg, Inj. Glycopyrrolate 4mcg/kg and Inj. Fentanyl 2mcg/kg. Pre-oxygenation with 100% oxygen was given for 3 min. Induction was done with Inj.Thiopentone 5-7 mg/kg, Inj. Succinylcholine 2 mg/kg. The trachea was intubated with cuffed Oro-tracheal tube of appropriate size. Loading dose of Inj. Atracurium 0.5mg/kg given. Anaesthesia was maintained with 50% N_2O in oxygen with 0.4-0.8% Isoflurane. Central venous catheter was inserted by modified saldinger's technique. After induction, Epidural catheter was inserted in lateral position. Before incision, 0.25% Inj. L-bupivacaine 10ml bolus dose was given in epidural catheter in Group-L and 0.25% L-bupivacaine plus Inj. Dexmedetomidine (10mcg) in total volume of 10ml bolus dose was given in Group-LD. Vitals at that time were noted. After 15 minutes, Epidural infusion of L-bupivacaine 0.125% (20 ml) and L-bupivacaine 0.125% plus

Inj. Dexmedetomidine 40mcg (20 ml) started @0.1 ml/ kg/hr. Intra-operative vitals like HR, BP noted every 15 minutes. Requirement of inhalational agents was adjusted according to the depth of anaesthesia, which was assessed by BIS score. PNS guided intermittent bolus dose of muscle

relaxant Inj. Atracurium 0.1 mg/kg was given. Epidural infusion continued until ureteric implantation was completed. Patients were reversed with Inj. Neostigmine 0.05 mg/kg + Inj. Glycopyrrolate 0.4 mg. After surgery, patients were shifted to post-transplant isolation room. Post-operatively vitals, pain and Modified Ramsay sedation score were observed for assessment of sedation at 0, 1, 2, 4, 8, 12, 18, 24 hours. If patient have pain (VAS>4) then additional dose of Inj. Tramadol 2 mg/kg epidural dose was given. Total requirement of rescue analgesia within 24hours was recorded.

Data Analysis has been done in SPSS V20.Continuous data are expressed as mean±sd form. Continuous data follows parametric and Non-Parametric data both. Independent t test and Mann Whitney test have been used for carrying out significant P-value. Chi Square test have been used for carrying out significant P-value. p-value < 0.05 considered to be statistically significant difference among groups.

Results

Intra-operative parameters:

Table 1: Heart Rate

TIME	GROUP-LD	GROUP-L	P value
Induction	90.63 + 10.69	90.50 + 8.18	0.95 (NS)
3 min	86.45 + 9.31	88.73 + 6.15	0.20 (NS)
6 min	84.88 + 10.15	87.30 + 6.21	0.20 (NS)
15 min	81.58 + 10.40	85.95 + 6.85	0.03*
30 min	76.90 + 10.42	85.50 + 6.36	<0.01*
1 hr	72.80 + 9.53	84.73 + 5.22	<0.01*
1 hr 30 min	70.38 + 8.89	83.95 + 6.34	<0.01*
2 hr	70.00 + 9.26	83.03 + 5.48	<0.01*
2 hr 30 min	69.85 + 6.87	82.38 + 6.34	<0.01*
3 hr	70.24 + 9.91	83.17 + 16.74	<0.01*
3 hr 30 min	73.00 + 8.12	87.55 + 8.26	<0.01*

Intra-operative pulse rate were lower in group-LD in comparison to group-L after giving bolus epidural dose and statistically significant (p<0.01*). Before the bolus epidural dose pulse rate were comparable to both the groups.

Table 2: Blood Pressure

TIME	GROUP-LD	GROUP-L	P value
Induction	146.73 ± 10.70	145.93 ± 10.03	0.73(NS)
3 min	142.48 ± 9.89	142.93 ± 9.80	0.84(NS)
6 min	140.45 ± 9.32	141.60 ± 10.21	0.60(NS)
15 min	131.08 ± 24.19	138.13 ± 8.27	0.09(NS)
30 min	133.05 ± 9.77	138.00 ± 8.00	0.02*
1 hr	129.33 ± 8.47	134.90 ± 6.11	<0.01*
1 hr 30 min	127.35 ± 8.31	134.48 ± 5.53	<0.01*
2 hr	124.43 ± 8.00	135.73 ± 6.07	<0.01*
2 hr 30 min	126.00 ± 7.00	136.80 ± 5.36	<0.01*
3 hr	128.62 ± 8.33	140.41 ± 5.73	<0.01*
3 hr 30 min	134.00 ± 9.30	146.27 ± 6.87	<0.01*

After giving bolus epidural dose the changes in blood pressure significantly lower in group-LD compare to group-L (p<0.02*).

Table 3: Inhalational Agent Requirement

TIME	GROUP-LD	GROUP-L	P value
Induction	0.73 + 0.19	0.88 + 0.16	<0.01*
3 min	0.69 + 0.23	0.89 + 0.14	<0.01*
6 min	0.63 + 0.25	0.85 + 0.15	<0.01*
15 min	0.56 + 0.21	0.79 + 0.16	<0.01*
30 min	0.48 + 0.21	0.77 + 0.17	<0.01*
1 hr	0.42 + 0.16	0.67 + 0.14	<0.01*
1 hr 30 min	0.35 + 0.17	0.66 + 0.14	<0.01*
2 hr	0.30 + 0.17	0.67 + 0.14	<0.01*
2 hr 30 min	0.25 + 0.11	0.58 + 0.20	<0.01*
3 hr	0.19 + 0.15	0.34 + 0.23	<0.01*
3 hr 30 min	0.10 + 0.10	0.18 + 0.06	0.02*

The total requirement of inhalational agent was statistically lower in the group-LD as compared with group- L at any point of time(p<0.02).

Table 4: Muscle Relaxant (Inj. Atracurium) Requirement

Total relaxant dose(mg)	GROUP-LD	GROUP-L	P value
Dose in mg	51.25 + 9.32	60.75 + 8.96	<0.01*

The total requirement of muscle relaxant dose is significantly lower in group-LD as compared to group-L throughout the surgery. The statistically significant difference was observed between two groups (p<0.01*)

Post- operative parameters:

Table 5: Heart Rate

TIME	GROUP-LD	GROUP-L	P value
0 hr	72.95 + 6.09	91.28 + 7.78	<0.01*
1hr	74.35 + 6.30	89.70 + 6.69	<0.01*
2 hr	77.05 + 6.39	91.23 + 7.91	<0.01*
4 hr	81.73 + 7.48	92.18 + 4.63	<0.01*
8 hr	86.33 ± 5.09	95.48 ± 6.21	<0.01*
12 hr	88.78 + 4.73	94.05 + 6.38	<0.01*
18 hr	89.23 + 6.19	92.50 + 8.77	0.11(NS)
24 hr	93.33 ± 5.80	93.50 ± 7.13	0.21(NS)

Post-operative pulse rate were lower in group-LD in comparison to group-L up to 12 hr and statistically significant difference (p<0.01*) and does not require any treatment.

Table 6: Blood Pressure

TIME	GROUP-LD	GROUP-L	P value
0 hr	132.10 ± 6.03	141.75 ± 7.22	<0.01*
1hr	131.90 ± 5.88	138.73 ± 6.26	<0.01*
2 hr	131.18 ± 4.71	140.20 ± 8.92	<0.01*
4 hr	133.05 ± 5.33	139.38 ± 10.10	<0.01*
8 hr	137.00 ± 4.67	141.30 ± 6.61	<0.01*

12 hr	140.00 ± 3.02	141.65 ± 4.72	0.14 (NS)
18 hr	141.13 ± 4.48	143.28 ± 6.68	0.26(NS)
24 hr	143.80 ± 5.66	143.25 ± 8.56	0.63(NS)

The changes in systolic and diastolic Blood Pressure were lower and significant in group-LD up to 8 hr ($p<0.02$*).After that they were comparable between the two groups and non-significant.

Table 7: Ramsay sedation Score

TIME	GROUP-LD	GROUP-L	P value
0 hr	3.88 + 0.56	3.38 + 0.59	<0.01*
1hr	3.43 + 0.64	3.15 + 0.53	0.03*
2 hr	3.40 + 0.59	2.95 + 0.45	<0.01*
4 hr	2.68 + 0.47	2.55 + 0.50	0.25(NS)
8 hr	1.73 + 0.55	1.70 + 0.46	0.93(NS)
12 hr	1.65 ± 0.58	1.60 ± 0.50	0.79(NS)
18 hr	1.65 + 0.58	1.53 + 0.51	0.37(NS)
24 hr	1.65 + 0.58	1.53 + 0.51	0.37(NS)

Ramsay sedation scores were higher in group-LD up to 3 hrs compare to group-L and statistically significant ($p<0.01$*).

Table 8: Post-operative Analgesia

	GROUP-LD	GROUP-L	P value
First dose (in hr)	7.03 ± 3.39	3.41 ± 2.90	<0.01*
Total dose (in hr)	1.58 ± 0.81	2.20 ± 0.76	<0.01*

The duration of requirement of first dose of rescue analgesia (Inj. Tramadol-2mg/kg) is significantly higher in group-LD (7.03+ 3.39 hr) compare to group-L (3.41 + 2.90hr) and statistically significant ($p<0.01$*). The requirement of rescue analgesia in 24hr were less in group-LD (1.58 + 0.81hr) in comparison to group- L (2.20 + 0.76hr)and it was statistically significant ($p<0.01$*).

Discussion

Renal transplantation is most effective renal replacement therapy for patients with end stage renal diseases (ESRD). While choosing an anaesthetic technique for any surgical procedure, desirable characteristics include stable hemodynamic parameters, minimal blood loss intraoperatively, early ambulation, good post-operative analgesia and lower incidence of various side effects. General anaesthesia has remained the most popular technique for renal surgeries because of the discomfort body position during prolonged renal procedures; Regional anaesthesia supplemented with good sedation has been advocated recently.

We have used dexmedetomidine as an adjuvant to epidural infusion of L-bupivacaine during intraoperative period. Addition of dexmedetomidine to local anesthetics associated with a rapid onset and establishment of action of local anesthetics, enhanced post-operative analgesia, dose sparing of local anaesthetics and lacks opioid related side effects. One of the remarkable properties of dexmedetomidine includes complete elimination by metabolism with hepatic extraction accounting for 70% of the metabolic pathway. Renal blood flow and renal clearance has no role to play in metabolism or elimination of dexmedetomidine as literacy reports confirmed no traces of unchanged dexmedetomidine in urine. These properties will provide another added advantage of dexmedetomidine to be used in regional anaesthesia in patients with deranged renal functions as compared with general anaesthesia.

A combined epidural and general anesthesia technique attenuate systemic hemodynamic changes due

to stress response and maintain stable vital parameters at different stages of surgery. The possible mechanisms are:

1. Reduced circulating catecholamines,
2. Better cardiac function due to decreased systemic vascular resistance,
3. Reduced volatile agents requirements and therefore less myocardial depression, and
4. Controlled preloading under CVP monitoring prior to reperfusion.

Dexmedetomidine leads to reductions in heart rate by increasing vagal tone and reducing sympathetic drive. **Bajwa *et al*** and **Neerja Bharti *et al*** also observed a more prominent reduction in heart rate and significant decreases in MAP approximately 30-35 minutes after the epidural injection of the drugs in patients receiving dexmedetomidine as compared with fentanyl.

We studied the effect of using epidural analgesia combined with general anesthesia guided by BIS monitoring on reduction of volatile agent requirement. During maintenance of anaesthesia, the BIS values were maintained in the range of 40-60 with isoflurane concentration 0.6-0.8%. When both groups were compared with each other, there was no statistically significant difference in BIS values and requirement of volatile anaesthetic was decreased in both groups but significantly decreased in group-LD ($p<0.02$)compare to group-L. Afferentation theory proposes that tonic sensory and muscles-spindle activity maintains a state of wakefulness. **Eappen and Kissin** proposed that decreased afferent input to the brain could lessen excitatory descending modulation of spinal cord motor neurons and suppress motor function. Thus, the combination of decreased inputs from sensory and motor afferents seen with epidural anaesthesia would be a reasonable mechanism for general anaesthetic effects and for decreased requirements of inhalational agents.

During combined general plus epidural anesthesia, the noxious stimulus originating from the surgical site is blocked at the spinal level, reducing the requirement of general anesthetics. In our study, requirement of muscle relaxant is decreased in both groups but it was statistically significant in group-LD (51.25 $\pm$ 9.32mg) than group-L (60.75 $\pm$ 8.96mg). Local anaesthetics in small doses depress post-tetanic potentiation. They have a direct effect on presynaptic, postsynaptic and muscle membrane, which may result in enhancement of neuromuscular block of both depolarising and non depolarising muscle relaxants, the mechanism that perhaps is responsible for the reduction in requirement of atracurium.

Postoperative pain scores were recorded by visual analogue scale ranging from 0 to 10 (0-no pain, 10-worst pain) at 0, 1, 2, 4, 8, 12, 18 and 24 hr. When vas score was $\geq$4, rescue analgesic tramadol 2mg/kg was given epidurally. In our study, duration of requirement of first post-operative rescue analgesia in group- LD was significantly higher(7.03 $\pm$ 3.39) compared to group-L (3.41 $\pm$ 2.90) and is statistically significant($P<0.01$*). Dexmedetomidine causes hyperpolarization of nerve tissues by altering transmembrane action potential and ion conductance at the brainstem locus ceruleus. It decreases the sympathetic outflow and norepinephrine release and mediates analgesic effects. The results of our study demonstrates that adding dexmedetomidine to 0.125% L-bupivacaine increases the duration of analgesia as well as decrease the requirement of postoperative analgesia compared to L-bupivacaine alone.

Sedation in the initial post-operative period is beneficial to the patient. The patients are not rendered unconsciousness thus retain spontaneous reflexes and cognitive responsiveness with early mobilization. Patients are sleepy but responding to loud noise and then verbal command. In our study, Ramsay sedation scores were higher in group-LD up to 3 hrs compare to group-L and statistically significant ($p<0.01$*).These sedative effects of dexmedetomidine are mediated by the activation of presynaptic α-2 adrenoreceptors in the locus coeruleus, which inhibit the release of norepinephrine.

Conclusion

The results of our study clearly indicate that dexmedetomidine is better adjuvant to L-bupivacaine as it has better hemodynamic stability, less requirement of muscle relaxant and inhalational agent,

longer duration of Post-operative analgesia and better sedation that is beneficial to the patients.

Conflict of interest: No

Source of funding: No

References

1. Shah VR, Butala BP, Parikh GP, Vora KS, Parikh BK, Modi MP, Bhosale GP, Mehta T. Combined epidural and general anesthesia for paediatric renal transplantation—a single center experience. InTransplantation proceedings 2008 Dec 1 (Vol. 40, No. 10, pp. 3451-3454). Elsevier.
2. Bajwa SJ, Kaur J, Singh BA. A comparative evaluation of epidural and general anaesthetic technique for renal surgeries: A randomised prospective study. Indian journal of anaesthesia. 2014 Jul;58(4):410.
3. Suryavanshi VS, Sahu A, Harde M. Efficacy of combined epidural general anesthesia for attenuating haemodynamic responses in gynaecological laparoscopic surgery. International Journal of Contemporary Medical Research. 2016;3:1354-8.
4. Gupta K, Rastogi B, Gupta PK, Jain M, Gupta S, Mangla D. Epidural 0.5% levobupivacaine with dexmedetomidine versus fentanyl for vaginal hysterectomy: A prospective study. Indian Journal of pain. 2014 Sep 1;28(3):149.
5. Bajwa SJ, Kaur J, Singh A. A comparative evaluation of epidural and general anaesthetic technique for renal surgeries : A randomised prospective study. Indian J Anaesthesia 2014;58:410-5.
6. Bajwa SJS, Arora V, Kaur J, et al. Comparative evaluation of dexmedetomidine and fentanyl for epidural analgesia in lower limb orthopedic surgeries. Saudi Journal of Anaesthesia. 2011;5:365–70.
7. Eappen S, Kissin I. Effect of subarachnoid bupivacaine block on anesthetic requirements for thiopental in rats. Anesthesiology 1998;88:1036–42.
8. Atia AM, Abdel-Rahman KA. Combined Thoracic Epidural with General Anesthesia vs. General Anesthesia Alone for Major Abdominal Surgery: Anesthetic Requirements and Stress Response. J Anesth Clin Res. 2016;7(616):2.
9. Usubiaga JE, Standaert F. The effects of local anesthetics on motor nerve terminals. J Pharmacol Exp Ther 1968;159:353–61.
10. Jaakola ML, Salonen M, Lehtinen R, Scheinin H. The analgesic action of dexmedetomidine—a novel α2-adrenoceptor agonist—in healthy volunteers. Pain. 1991 Sep 1;46(3):281-5.