METHEMOGLOBIN LEVELS DURING EPIDURAL ANESTHESIA FOR RENAL TRANSPLANTATION

- Comparison of Prilocaine with Bupivacaine -

HALE BERKSUN[*], ELIF A. AKPEK[**]
AND GÜLNAZ ARSLAN[***]

Abstract

Background and objective: One goal of anesthesia for renal transplantation is to avoid an excess load to be imposed on the newly functioning kidney, by using appropriate agents and dosages in the perioperative management. The purpose of this study was to investigate the effect of prilocaine on serum methemoglobin levels when used as the local anesthetic in epidural anesthesia for renal transplantation, and to compare its effects with that of bupivacaine, which is the standard local anesthetic used.

Methods: 26 adult renal recipients were randomized into 2 equal groups according to the local anesthetic used for epidural anesthesia during the operation. Patients in group P (n = 13) were given prilocaine and those in group B (control, n = 13) received bupivacaine. The methemoglobin measurement intervals were at: baseline before administration of local anesthetic, and then at 2 hours, 5 hours, and 12 hours of local anesthetic administration.

From Dept. of Anesthesiology Başkent University Faculty of Medicine, 06490-Ankara, Turkey.
* Specialist.
** Assoc. Prof.
*** Professor of Anesthesiology.
Correspondence: Elif A. Akpek, MD, Department of Anesthesiology, Başkent University Faculty of Medicine, Bahcelievler 06490-Ankara, Turkey. Tel: (90) 312 2126868/1172, Fax: (90) 312, E-mail: elifakpek@baskent-ank.edu.tr.

Results: Methemoglobin levels in the prilocaine group were above the normal range in all measurements other than baseline. In the bupivacaine group, methemoglobin levels increased only at 5 hours of local anesthetic administration. However, methemoglobin concentrations and hemoglobin levels were comparable between the two groups at all time intervals, and none of the patients demonstrated clinical symptoms.

Conclusion: The use of prilocaine in epidural anesthesia for renal transplantation surgery resulted in an increase in methemoglobin levels, which did not cause any clinical symptoms and was similar to those of bupivacaine at all time measurements.

Keywords: Surgery: renal transplantation; anesthesia: epidural anesthesia; local anesthetics: prilocaine; methemoglobinemia.

Introduction

In majority of the transplantation centers, the anesthetic method of choice for renal transplantation is general anesthesia owing to its airway management safety, higher surgeon satisfaction, patient comfort and organ protection[1-4]. In contrast, increasing numbers of centers, however, appear to prefer regional techniques, because of its lower toxicity profiles and its ability to avoid many of the complications associated with general anesthesia.

The renal transplantation program at our Centre was established in 1985. To date, we have used general anesthesia for recipient procedures in more than 1.500 renal transplantation cases. In July 1998, we introduced the use of continuous epidural anesthesia with bupivacaine (Marcaine) for kidney recipients[5]. To date, it has been safely used in more than 300 recipients[6,7]. There have been no coagulopathic and/or neurological complications, and it has become the standard anesthetic protocol for renal transplantation at our Institution, unless there is an absolute contraindication and/or patient reluctance to its use. However, owing to the potential risk of increased sensitivity to cardiotoxicity with bupivacaine secondary to metabolic alterations, presence and/or progression of hyperkalemia, or

coexisting cardiovascular changes in chronic renal failure patients, other local anesthetics are being sought. Prilocaine (Citanest) has been looked at as an alternative. The major drawback to using prilocaine is its potential risk of methemoglobinemia, which is actually a rare complication that is mostly seen after administration of high doses.

The purpose of this study was two fold:

(1) To assess the effect of prilocaine on serum methemoglobin levels when used in epidural anesthesia for renal transplantation.

(2) Compare this effect with that of bupivacaine (Marcaine); considered as the standard local anesthetic, when used in the same technic.

Patients and Methods

Following approval of the Institution's Ethical Committee and obtaining patients' informed consents, 26 adult patients with chronic renal failure (ASA 3) to undergo cadaveric or living-related renal transplantation, were enrolled in this prospective, randomized, controlled study. Patients were randomized into two equal groups according to the local anesthetic used for epidural anesthesia during the operation. Patients in Group P (n = 13) were given prilocaine (Citanest®), and those in Group B (control, n = 13) received bupivacaine (Marcaine®).

Preoperatively, all recipients were assessed using the standard protocol of the Başkent University Transplantation Programme, and all required consultations were completed. Whether surgery was scheduled on an emergent or an elective basis, patients were informed about the anesthetic technique to be used and gave their consent to proceed. Individuals who refused regional anesthesia and those with abnormal coagulation parameters were not included in the study. All recipients had undergone unheparinized hemodialysis in their last several sessions and had normal prothrombin/ INR values prior to surgery.

Each individual was premedicated with oral midazolam (0.1 mg/kg) 1 hour prior to surgery. In the operating room, intravenous (i.v.) access via

an 18 - to 20 – gauge catheter was secured on the arm opposite the one in which the arteriovenous fistula exists, and an infusion of 0.9% saline solution was initiated. Standard monitoring included; ECG, heart rate, non-invasive blood pressure measurements, and peripheral oxygen saturation (SpO_2). After additional i.v. midazolam (1-2 mg) was given, a radial arterial catheter was inserted on the same side as the i.v. catheter to obtain arterial blood samples during the study. Central venous catheterization was not performed.

Standard epidural anesthesia technique was used in all patients. The procedure was performed by an experienced anesthesiologist in all cases. After appropriate patient positioning and sterile conditions, a 16 – or 18 – gauge Touhy needle was inserted at the T12-L1 or the L1-2 intervertebral space by using a loss of resistance technique with saline, and an epidural catheter was advanced 4-6 cm cephalad. The occurrence of any traumatic attempts or dural punctures were accepted as exclusion criteria and conversion to general anesthesia was resorted to. After the epidural catheterization was achieved, patients were turned back to the supine position and given supplemental nasal oxygen until the end of surgery.

In Group P (prilocaine, n = 13), patients were given 20 mL of 2% prilocaine in combination with 50 μg of fentanyl administered epidurally. One hour after the first epidural injection, a bolus of 10 mL prilocaine 1% was given, and a maintenance infusion of prilocaine 1% was started at a rate of 7 mL/hour until the end of the operation. Patients in Group B (bupivacaine, n = 13) acted as a control. They received 20 mL of 0.5% bupivacaine in combination with 50 μg fentanyl administered epidurally. Two hours after the first epidural injection, a bolus of 10 mL of bupivacaine 0.5% was given, and the maintenance infusion of bupivacaine 0.25% was started again at a rate of 7 mL/hour until the end of the operation. In cases where additional analgesic was required, 5 mL of 1:1 diluted concentration of each drug was given in both groups.

Intraoperatively, patients were sedated to the level of “awake and calm” or “eyes closed, responded to verbal commands” using intermittent i.v. midazolam as needed. Oxygen was administered via a nasal cannula

throughout surgery. Each individual received i.v. methylprednisolone and antibiotics at induction, and i.v. mannitol (0.5 g/kg) and furosemide (1 mg/kg) during vascular anastomosis.

Once the procedure was completed, the patient was transported to the Transplantation Unit. All patients were prescribed the Hospital's standard immunosuppressive regimen postoperatively, and the initial doses of cyclosporine-A (8 mg/kg), prednisolone (1.5 mg/kg), and azathioprine (2-3 mg/kg) were adjusted appropriately during follow-up.

Postoperative pain control was initiated using patient-controlled epidural analgesia (PCEA) with morphine. The epidural catheter was removed on postoperative day 2 at the latest.

Serum methemoglobin levels were measured at 4 time intervals based on the duration of local anesthetics' action and methemoglobin kinetics obtained from the literature: at baseline before administration of local anesthetic (t1), at 2 hours (t2), 5 hours (t3), and 12 hours (t4) of local anesthetic administration. Methemoglobin was measured by the spectrophotometric method using the cyanohematin method. The maximal absorption of methemoglobin is 630 nm. Methemoglobin values were given as percentages of hemoglobin concentration and those less than 1% was accepted as normal. Concomitant measurement of lactate levels, analysis of arterial blood gases, and recording of hemodynamic parameters were done. Other data collected were total amount of intraoperative local anesthetics and sedatives used, and need for vasoactive drugs either in hyper – or hypotensive episodes. Each individual was monitored postoperatively for neurological as well as other complications related to the anesthetic technique. The need for dialysis and incidence of acute rejection were also recorded.

To calculate the sample size needed to conduct the investigation, serum methemoglobin level was selected as the primary outcome measure, and the differences between the groups were calculated on the basis of findings from previous studies and on clinical relevance. We used these differences to calculate the sample size required to give the trial a power of 80% (for $\alpha < 0.05$). Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 10, SSPS

Inc, Chicago, IL, USA). The Friedman and Wilcoxon tests were used to analyze dependent variables, and the Mann-Whitney *U* test was used to compare independent variables. All data are presented as mean ± SD, and values for *P* less than 0.05 were considered statistically significant.

Results

Demographic characteristics of the recipients are presented in Table 1.

Table 1
Demographic and surgical characteristics

	Group P (Prilocaine)	Group B (Bupivacaine)
N	13	13
Age (year)	32.4 ± 9.6	32.4 ± 11.0
Sex (F/M)	2/11	6/7
Weight (kg)	63.0 ± 10.0	57.5 ± 13.5
Duration of chronic renal failure (years)	2.8 ± 2.7	3.0 ± 2.8
Duration of hemodialysis (years)	2.6 ± 2.7	2.7 ± 2.8
Duration of operation (hours)	5.6 ± 0.7*	5.0 ± 0.4
Source of organ (living-related/cadaveric)	11/2	9/4

Data are presented as means ± SD or number.
* $P < 0.05$ compared with group B.

Total amount of intraoperative local anesthetic used was 1093 ± 166 mg (3.1 = 0.6 mg/kg/h) in the prilocaine group and 257 ± 39 mg (0.9 ± 0.2 mg/kg/h) in the bupivacaine group. These total amounts included the additional requirements in the groups (11 patients in prilocaine *vs*. 7 patients in bupivacaine group, $P > 0.05$).

Methemoglobin levels and their ratios to total hemoglobin increased throughout the operation in both groups, and the trends appeared parallel. Methemoglobin levels were above the normal range at all time measurements other than baseline in the Prilocaine group, whereas they were above normal only at the 5-hour measurement in the Bupivacaine

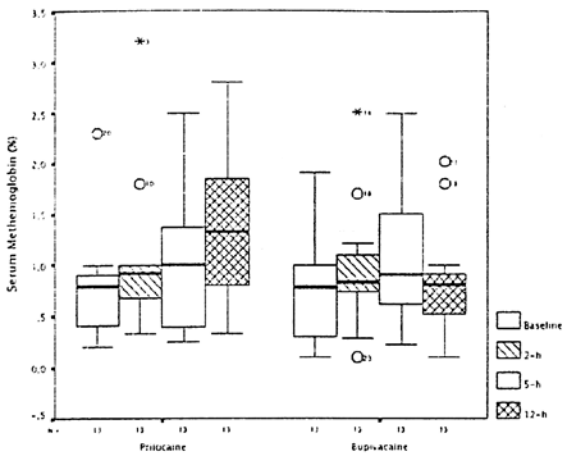
group. Postoperative levels at 12 hours after surgery demonstrated further increased values in the Prilocaine group, whereas the levels decreased in the Bupivacaine group. However, mean levels at all time measurements and number of patients with higher-than-normal methemoglobin levels were similar between the groups ($P > 0.05$) (Table 2, Figure 1). None of the patients in either group revealed clinical symptoms indicating methemoglobinemia. Total hemoglobin values were comparable between the groups ($P > 0.05$) (Table 2).

Table 2
Methemoglobin (metHb) and hemoglobin levels and methemoglobin percentages

		Baseline	**2 hours**	**5 hours**	**12 hours**
Hb (g/dL)	Prilocaine	11.4 ± 1.7	10.8 ± 1.6	10.8 ± 1.6	10.2 ± 1.7
	Bupivacaine	11.2 ± 1.3	10.7 ± 1.1	10.9 ± 0.9	10.7 ± 1.2
MetHb (g/dL)	Prilocaine	0.10 ± 0.08	0.11 ± 0.07	0.12 ± 0.08	0.14 ± 0.09
	Bupivacaine	0.08 ± 0.06	0.11 ± 0.07	0.12 ± 0.08	0.08 ± 0.06
MetHb (%)	Prilocaine	0.88 ± 0.67	1.03 ± 0.75	1.11 ± 0.73	1.36 ± 0.79
	Bupivacaine	0.74 ± 0.52	0.98 ± 0.60	1.14 ± 0.71	0.82 ± 0.55

Data are presented as means ± SD.
Hb: Hemoglobin, MetHb: Methemoglobin.
$P > 0.05$.

Fig. 1
Methemoglobin levels in two groups



Hemodynamic data recorded at the same time intervals with the methemoglobin measurements revealed values in the clinically normal range in both groups. There were no differences between the groups in terms of systolic (SAP), diastolic (DAP), and mean blood pressures (MAP) at any time measurements. Heart rates were higher in the Bupivacaine group at the 5-hour interval (86 ± 15 vs. 75 ± 7 bpm, $P = 0.03$). However, peripheral oxygen saturations were significantly lower in the Prilocaine group at all time measurements other than baseline ($P < 0.05$) (Table 3). Within-group comparisons reveal: systolic blood pressures at 2 hours were lower in both groups relative to baseline values. Heart rates were also lower at the 2-hour measurement when compared with all others in both groups. Peripheral oxygen saturation decreased significantly over time in the Prilocaine group; in contrast, intraoperative (2- and 5-hour) measurements in the Bupivacaine group revealed significantly higher values ($P < 0.05$) (Table 3).

Table 3

Hemodynamic parameters in the P & B Groups

		Baseline	**2 hours**	**5 hours**	**12 hours**
SAP (mmHg)	Prilocaine	133 ± 11	125 ± 13	134 ± 14	135 ± 17
	Bupivacaine	134 ± 31	122 ± 22	126 ± 15	131 ± 22
DAP (mmHg)	Prilocaine	81 ± 9	78 ± 12	85 ± 11	80 ± 9
	Bupivacaine	85 ± 19	76 ± 19	77 ± 11	80 ± 20
MAP (mmHg)	Prilocaine	99 ± 8	94 ± 10	101 ± 10	98 ± 11
	Bupivacaine	101 ± 22	91 ± 19	93 ± 11	97 ± 20
HR (bpm)	Prilocaine	76 ± 14	67 ± 10	75 ± 7†	79 ± 10
	Bupivacaine	84 ± 19	73 ± 17	86 ± 15	81 ± 13
SpO_2 (%)	Prilocaine	97.5 ± 2.8	96.5 ± 2.5*	95.0 ± 2.9*	93.1 ± 2.7*
	Bupivacaine	98.4 ± 1.9	99.3 ± 1.1	99.1 ± 1.2	97.3 ± 2.5

Data are presented as means ± SD.

SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, HR: Heart rate, SpO_2: Peripheral oxygen saturation.

† $P < 0.05$ compared with group B.

** $P < 0.01$ compared with group B.

Arterial blood gas analyses of patients are presented in Table 4. There were no significant differences in any measurements between the groups. However, within – group comparisons, revealed significantly lower pH values and higher arterial oxygen saturation (SaO_2) and pO_2 values at 2- and 5-hour samples when compared with baseline and 12-hour measurements in both groups ($P < 0.01$). All these changes in the 2 groups appeared parallel but only changes in SpO_2 values were significantly different within the Prilocaine group ($P < 0.01$). Serum lactate levels were similar at all time measurements both between and within the groups, and they were all within the normal range (Table 4).

Table 4

Lactate values and arterial blood gas analysis in the P & B Groups

		Baseline	**2 hours**	**5 hours**	**12 hours**
Lactate (mmol/L)	Prilocaine	2.3±1.2	2.3±1.2	2.2±1.1	2.4±0.9
	Bupivacaine	1.8±0.5	1.9±0.7	2.5±0.7	2.0±0.7
PH	Prilocaine	7.37±0.05	7.32±0.04	7.28±0.04	7.40±0.04
	Bupivacaine	7.36±0.06	7.31±0.05	7.29±0.05	7.38±0.07
pO_2 (mmHg)	Prilocaine	81.8±17.4	131.2±31.2	145.3±49.2	80.9±23.4
	Bupivacaine	100.0±30.9	140.5±45.5	124.3±38.1	80.6±9.3
pCO_2 (mmHg)	Prilocaine	43.2±5.0	46.0±8.4	48.9±8.5	38.7±3.7
	Bupivacaine	42.6±5.8	46.3±7.0	45.1±5.1	40.6±4.3
SaO_2 (%)	Prilocaine	95.0±2.3	98.5±1.1	97.6±2.4	94.3±3.1
	Bupivacaine	96.0±3.7	98.2±1.6	97.6±2.2	95.6±1.4
BE	Prilocaine	1.0±5.5	-1.2±6.4	-2.0±4.7	0.1±3.9
	Bupivacaine	-0.1±5.9	-1.6±5.4	-3.6±3.4	0.5±6.7
Het (%)	Prilocaine	41.3±6.7	37.0±5.4	37.0±6.4	38.1±7.0
	Bupivacaine	40.5±7.5	38.0±5.4	38.4±5.8	38.0±6.0

Data are presented as means ± SD.

pO_2: Partial oxygen pressure, pCO_2: Partial carbon dioxide pressure, SaO_2: Arterial oxygen saturation, BE: Base deficit/excess, Het: Hématocrit.

$P > 0.05$.

Total amount of intraoperative fluid used did not differ in the 2 groups (5.7 ± 1.8 mL/kg/h in Group P and 6.5 ± 2.1 mL/kg/h in Group B) ($P > 0.05$). Urine output after completion of vascular anastomosis was also similar (2.3 ± 1.4 mL/kg/h in Group P and 2.7 ± 1.8 mL/kg/h in Group B) ($P > 0.05$). One patient in the Bupivacaine group required a vasopressor agent for treatment of a transient hypotensive episode, and 2 patients were given antihypertensive drugs. None of the recipients were administered colloid or blood products. Total midazolam requirement was 11.2 ± 4.4 mg in the Prilocaine group and 8.3 ± 3.6 mg in the Bupivacaine group ($P > 0.05$).

There were no traumatic attempts or dural punctures in either group, and no intraoperative complications were encountered in any patient.

As for postoperative complications, hematoma at the surgical site developed in one patient in the Prilocaine group and in two patients in the Bupivacaine group.

Infection at the surgical incision site was observed in only one patient in the Bupivacaine group. There were no differences regarding the need for hemodialysis or incidence of acute rejection episodes postoperatively. There were no neurological and/or coagulopathic complications in any patients. There was no mortality.

Discussion

Anesthesia for renal transplantation requires minimal toxicity for patient and graft, maintenance of vital functions, and sufficient pain relief. Anesthetic management in these patients must also target avoiding excess load on the newly functioning kidney by using appropriate agents and dosages for postoperative analgesia. This requires that the anesthesiologist should have a sufficient, up-to-date knowledge and experience with the pathophysiology of chronic renal failure.

This study investigated the use of prilocaine in epidural anesthesia for renal transplanation and assessed its effect on production of

methemoglobinemia. Patients anesthetized with epidural bupivacaine as standard Department protocol, acted as controls. The authors' experiences with epidural anesthesia have been satisfactory; any anesthetic-related complications or coagulopathic/neurological complications were not encountered during the last 7 years[5-7].

In this study, baseline methemoglobin levels in both groups were within the normal range. Thereafter, levels in the Prilocaine group increased to above normal at all time measurements, and levels in the Bupivacaine group were above normal at the 5-hour measurement. The normal range of methemoglobin concentration defined as less than 1% in this study, is controversial. Other reports suggest that the upper limit is 2%[8,9]. All values recorded as above normal in this study were less than 2% at all time measurements. There were no clinical symptoms at any time in either group. Severe clinical symptoms appear when methemoglobin percentages rise above 10%. However, anemia associated with chronic renal failure can mask the appearance of clinical cyanosis. Anemia increases sensitivity to the effects of methemoglobinemia by decreasing oxygen carrying capacity[10].

Methemoglobin levels reach peak values at 3-4 hours after local anesthetic administration and remain elevated for 12-14 hours[10]. Continuous absorption, increased half-life, and toxic metabolites can prolong the methemoglobinemia state. In this study, co-existing chronic renal failure, continuous local anesthetic infusion and ischemia/reperfusion model were the contributing factors that might potentially prolong this duration.

In contrast to low levels of methemoglobin in the Bupivacaine group, 12-hour values in the Prilocaine group led to the following speculations:

1) These might be the final peak values, which will decrease to normal levels from this point forward (supported by the knowledge of methemoglobin metabolism as given above).

2) These levels might indicate the limit of the methemoglobin increase due to initiation of function of the newly transplanted kidney (prilocaine otherwise might have caused even higher levels in chronic

renal failure patients), or

3) These might indicate an increasing trend that continues until peak levels are achieved.

A decreasing trend in methemoglobin values in the Prilocaine group was not observed in this study and therefore, all 3 speculations above will remain unsolved, and the safety of prilocaine in chronic renal failure and / or renal transplant patients cannot be suggested with these data. In addition, data in this study are not sufficient to present the relationship of initiation of renal function with reperfusion after transplantation and changes in metabolism of local anesthetics.

The safe therapeutic ranges for local anesthetics are classically presented as maximum dose per single use. However, in cases of continuous infusion and/or additional bolus doses, maximum infusion rates per hour or maximum total doses per day have not been defined. Therefore, authors cannot show and/or comment on where the total doses of both local anesthetics used in this study lie with respect to their maximum limits.

Hemodynamic data were similar and within the normal range in both groups. Arterial oxygen saturations (SaO_2) and pO_2 values were high at the 2- and 5-hour measurements in both groups because nasal oxygen support was given to all patients during the operation. Peripheral oxygen saturation (SpO_2) values recorded at the same time measurements also were high in the Bupivacaine group. However, SpO_2 values in Prilocaine group revealed gradual decreases over time that might be related to increasing methemoglobin levels[11]. In both groups, pH values at the 2- and 5-hour measurements were lower than those measured at baseline and postoperative measurements and these findings might be explained with either one or more than one of the factors such as the use of preoperative dialysis, metabolic changes secondary to intraoperative ischemia/reperfusion injury and increased pCO_2 values secondary to sedation. Standard anesthesia protocol with these patients did not include placement of central venous catheter. However, maintenance fluid replacement and urine output were within normal range as calculated per kilogram basis, thus intravascular

volume status appeared to be sufficient. Lactate levels were also studied to evaluate metabolic status in this study and all measurements in both groups were within normal range.

Some antihypertensive agents (e.g., isosorbide dinitrates, β-blockers) and metabolic acidosis can enhance development of methemoglobinemia in patients with chronic renal failure[12]. In addition, decreased protein binding and increased free fraction of drugs can increase the risk of methemoglobinemia[13]. Moreover, administration of immunosuppressive drugs, such as cyclosporine, in patients with transplanted kidneys can cause hepatic dysfunction leading to decreased local anesthetic clearance and further increase the risk of methemoglobinemia[10]. It has been also demonstrated that bupivacaine at normal doses can lead to cardiotoxic adverse effects when used in patients with terminal renal failure[14].

There are few studies investigating methemoglobinemia with use of bupivacaine[10,15-17]. Of them, only one compared bupivacaine and prilocaine for axillary blockade in a prospective randomized controlled design. However, the primary outcome measure in that study was analgesic effect, and methemoglobinemia was not noted as an important consideration[16]. Bupivacaine has been presented as the cause of methemoglobinemia in two cases, both of which were associated with chronic renal failure[10,15]. These cases support the ideas of the present study in which alternative local anesthetics ought to investigated in renal transplantation cases.

Although prilocaine has been suggested as a frequent cause of methemoglobinemia, it does so at higher doses and with coexisting factors such as increased age, metabolic status, and drug combinations. Methemoglobinemia studies of prilocaine largely appear to be case presentations, and the majority includes circumcision procedures of newborns with EMLA®. A literature search for the relationship of prilocaine and methemoglobinemia revealed eight prospective randomized controlled trials[16,18-26]. Three suggested the safe use of EMLA® in circumcision procedures of newborns[18-20]. Others included use of prilocaine for regional blockade in adults. Only one revealed a 16%-17% rate of occurrence of methemoglobinemia in 3 of 20 patients when 700 mg of 1% prilocaine

was used for siatic/3-in-1 block[22]. Another study investigated the safety of different pulse oxymeters in 130 patients in whom plexus blockade with prilocaine was performed and suggests that normal SaO_2 values associated with low SpO_2 values indicate methemoglobinemia; this requires further evaluation with a CO-oxymeter for more accurate data[23].

In conclusion, use of prilocaine for epidural anesthesia in patients undergoing renal transplantation revealed clinically unimportant increases in methemoglobin levels during 12-hour postoperative follow-up. Comparison of these levels with bupivacaine levels showed no significant differences in any time measurements. However, increasing trends of methemoglobin at the last measurements and decreasing SpO_2 values in spite of the normal SaO_2 values in the Prilocaine group remain controversial points in this study. To assure safe use of epidural prilocaine in renal transplantation cases, future studies should be designed using larger series of patients to investigate serum local anesthetic concentrations and methemoglobin trends, observing patients for longer times, and comparing these data with those of healthy individuals.

References

1. Lincke CL, Merin RG: A regional anaesthetic approach for renal transplantation. *Anesth Analg*; 55:69-73, 1976.
2. Sear JW: Anaesthesia for patients undergoing renal transplantation. In: Morris PJ (Ed) *Kidney Transplantation Principles and Practice*. 5th ed., WB Saunders Company, USA. 184-5, 2001.
3. Firestone L, Firestone S, Feiner JR, Miller RD: Organ transplantation. In: Miller ED, Reves JG, Roizen MF, Savarese JJ (Eds). *Anesthesia*; 5th ed., Churchill Livingstone, USA, 1982-83, 2000.
4. Zacharias, Gilmore I, Herbison G, Sivalingam P, Waler R: Interventions for protecting renal function in the perioperative period. *Cochrane Database Syst Rev*; 20(3):CD003590, 2005.
5. Akpek EA, Kayhan Z, Kaya H, Candan S, Haberal M: Epidural anaesthesia for renal transplantation: A preliminary report. *Transpl Proceedings*; 31:3149-50, 1999.
6. Arslan Akpek E, Kayhan Z: Patient-controlled Epidural Analgesia with Morphine in Renal Transplant Patients. *Transplantation Proceeding*; 32:613-5, 2000.
7. Akpek EA, Kayhan Z, Dönmez A, Moray G, Arslan G: Early postoperative renal function following renal transplantation surgery: effect of anesthetic technique. *Journal of Anesthesia*; 16:114-8, 2002.
8. Griffin JP: Methaemoglobinemia. *Adverse Drug React Toxicol Rev*; 16:45-63, 1997.
9. Dougles WW, Fairbanks VF: Methaemoglobin induced by a topical anaesthetic spray (cetacaine). *Chest*; 71:587-591, 1977.
10. Hardwick FK, Beaudreay RW: Methaemoglobinemia in a renal transplant patient: case report. *Pediatric Dentistry*; 17:460-3, 1995.
11. Morgan GE, Mikhail MS: Respiratory physiology and anaesthesia. In: *Clinical Anesthesiology* (Morgan GE, Mikhail MS, Murray MJ, Eds). 3rd ed. Lange/Mc Graw-Hill, New York, 432-434, 2002.
12. Arsura E, Lichstein E, Guadagnino V, Nicchi V, Sanders M: Methaemoglobin levels produced by organic nitrates in patients with coronary artery disease. *J Clin Pharmacol*; 24:160-4, 1984.
13. Conrad KA, Byers JM, Finley PR, Burnham L: Lidocaine elimination: effects of metoprolol and of propanolol. *Clin Pharmacol Ther*; 33:133-138, 1983.
14. Gould DB, Aldrete JA: Bupivacaine cardiotoxicity in a patient with renal failure. *Acta Anesthesiol Scand*; 27:18-21, 1983.
15. Schroeder TH, Dieterich HJ, Muhlbauer B: Methaemoglobinemia after axillary block with bupivacaine and additional injection of lidocaine in the opertive field. *Acta Anaesthesiol Scand*; 43:480-2, 1999.
16. Tryba M, Borner P: Clinical effectiveness and systemic toxicity of various mixtures of prilocaine and bupivacaine in axillary plexus block. *Reg Anaesth*; 11:40-9, 1988.
17. Rupieper N, Stocker L: Met-Hb formation and local anaesthesia using bupivacaine, carticaine and etidocaine. *Anaesthesist*; 30:23-5, 1981.
18. Stevens B, Johnston C, Taddio A, et al: Management of pain from heel lance with lidacaine-prilocaine (EMLA) cream: is it safe and efficacious in preterm infants? *Jdev Behav Pediatr*; 20:216-21, 1999.
19. Brisman M, Ljung BM, Otterbom I, et al: Methaemoglobin formation after the use of EMLA cream in term neonates. *Acta Paediatr*; 87:1191-4, 1998.
20. Taddio A, Stevens B, Craig K, et al: Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. *N Engl J Med*; 336:1197-201, 1997.
21. Wagner F, Missler B: Combined 2-in-1 sciatic block. Prilocaine 500 mg vs 650 mg. *Anaesthesist*;