BANTAO Journal 2021; 19(1): 14-19

BJ

BANTAO Journal

Original article

Analgesia in Kidney Transplant Recipients

Aleksandra Gavrilovska-Brzanov[1], Sasho Dohchev[2], Sotir Stavridis[2], Aleksandra Panovska Petrusheva[1], Marija Srceva Jovanovski[1], Biljana Kuzmanovska[1], Toni Risteski[3], Ognen Ivanovski[2], Nikola Brzanov[1] and Goce Spasovski[4]

[1]University Clinic for Traumatology, Orthopedic Disease, Anesthesiology, Reanimation and Intensive Care Medicine and Emergency Department, [2]University Clinic for Urology, [3]University Clinic for Pediatric Surgery, [4]University Clinic for Nephrology, Faculty of Medicine, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia

Abstract

Introduction. To our knowledge, currently no consensus or guidelines exist regarding perioperative and postoperative analgesia management in renal transplant recipients.
Methods. We conducted an observational prospective clinical study to evaluate the analgesia management practice in kudney transplant recipients. All consecutive patients who underwent kidney transplant surgery were enrolled in this observational clinical study. According to current analgesia management practice in our institution, patients were divided in two groups: patients who received general anesthesia and epidural analgesia were group E, and patients who received general anesthesia and i.v. analgesia were group G. The primary outcome measure in this study was VAS score and 24 h analgesia requirements. The second outcome measures were complications and/or side effects related to analgesia treatment.
Results. Group E had lower VAS pain score both at rest and on movement but only in the first 2 h, (VAS at rest E. 3.1±0.3 vs. G. 4.0±0.3, VAS on movement E. 4.2±0.6 vs. G. 4.5±0.3, $p<0.05$). The pain score by VAS scale did not differ between the groups at 6 h, 12 h and 24 h postoperatively, p=NS. Additionally, a small difference was noticed in side effects. Patients in group E had reported more side effects than patients in group G.
Conclusion. The study highlighted the variety in clinical practice regarding anesthesiologist preferences for pain management in kidney transplant recipients. This evaluation did not show any difference between anesthetic techniques and clinical results.

Keywords: kidney transplant, analgesia, epidural, analgesia management

Introduction

In our country since 1977 kidney transplant has been the preferred treatment of patients with end-stage kidney disease [1,2]. For optimizing surgical outcome adequate analgesia treatment in renal transplant recipients requires satisfactory pain relief, maintenance of physiological homeostasis and minimal nephrotoxicity [1,3,4]. To our knowledge, currently no consensus or guidelines exist regarding perioperative and postoperative analgesia management in renal transplant [5]. A significant number of clinical research is investigating the analgesia management, but the majority of these studies exclude renal transplant recipients [6], resulting in a limited evidence-based analgesia management in this complex patient cohort [5]. Many different strategies and techniques have been reported in the literature [1,3]. These patients usually are managed with a combined general and regional anesthesia. Many anesthesiologists avoid regional anesthesia due to concerns regarding coagulation disorders in kidney disease patients. As well as use of anticoagulant drugs before surgery due to comorbidities and use of anticoagulants intraoperative and postoperative for improving graft survival [7].

Material and methods

In our hospital, there is heterogeneity in management of analgesia in renal transplant recipients. Therefore, to provide an evidence-based management, we conducted an observational clinical study in order to encompass the entire perioperative and postoperative period and to generate an overview of current practice and to evaluate the efficacy of different analgesia regimens.
Hospital Ethics Committee approval and patient written informed consent were obtained before the beginning of the study. Every patient who underwent open surgery for kidney transplant during the period of

Correspondence to: Aleksandra Gavrilovska-Brzanov, University Clinic for Traumatology, Orthopedic Disease, Anesthesiology, Reanimation and Intensive Care Medicine and Emergency Department, 1000 Skopje, R. N. Macedonia; Phone: +389 71 24 07 01; E-mail: gavrilovska.aleksandra@gmail.com

January 2019 until August 2020was enrolled in the study. Excluded from the study were patients with any psychiatric disorder. The American Society of Anesthesiologist (ASA) score was assessed in all patients. The observers providing postoperative evaluation of patients were unaware of the type of anesthesia and analgesia method. According to current analgesia management practice in our institution, patients were divided in two groups: Group E (patients who received a combined general anesthesia and epidural analgesia) and Group G (patients who received only general anesthesia and i.v. analgesia). All patients did not eat or drink after midnight the night before surgery and premedication with Diazepam 5 mg orally was administered 2 h before surgery. A standard hemodynamic monitoring [electrocardiogram, pulse-oximetry, non-invasive blood pressure] was made before induction in anesthesia. According to patient's medical history, physical examination, medical analysis and anesthesiologist preferences, the analgesia technique was determined. Epidural catheter was placed in Group E, before induction in anesthesia. Patients who received epidural were in a sitting position L1-L2, epidural space was identified and with Touhy 18G needle and loss of resistance technique epidural catheter was placed. Afterwards negativity was confirmed with bupivacaine 0.5%-2 ml and as loading dose fentanyl 0.1 mcg was used. All patients were induced in anesthesia according to institutional protocol with midazolam 1 or 2 mg, fentanyl 2-10 mcg/kg, propofol 1-2 mg/kg and atracurium 0.5 mg/kg. Volume guarantied/pressure controlled mechanical ventilation (Datex-Ohmeda Avance S-5) with PEEP 5-7 cmH_2O and mixture of 50% oxygen/air was placed. Respiratory rate and tidal volume from 6-8 ml/kg were adjusted according to end-expiratory CO_2 (Et CO_2) and arterial blood gas analyses. Intra-arterial line and central venous line with continuous invasive pressure measurements were placed. Anesthesia was maintained with total intravenous anesthesia (remifentanil 0.25-0.5 mcg/kg/min and propofol 0.5-1 mg/kg). Except received fentanyl as loading dose in the epidural catheter in E group, nothing else was used until the end of surgery, when patients were transferred to transplantation unit and the time for the first analgesia requirement was noted. At the time of analgesia requirement, in group E continuous infusion with bupivacaine 0.125% and morphine 0.1 mg/ml was given starting with 2 ml/h. In group G after remifentanyl infusion was discontinued in the end of surgery if there was need of rescue analgesia fentanyl was used in 0,001 mcg/kg and patients were transferred to transplantation unit. The time for the first analgesia requirement was noted and the anesthesiologist and nephrologist in charge prescribed analgesics drugs.

We observed and analyzed the following parameters: patient demographic data, analgesia management in terms of time, dose, technique, anesthesia time and surgical time. Patients graded their pain on a visual linear analog scale (Visual Analogue Scale-VAS) of 1-10. VAS was noted at rest and during mobilization at 2 h, 6 h, 12 h, and 24 h postoperatively. Time for the first rescue analgesic was noted and total analgesic drugs received during 24 h. Any complication and side effects related to analgesia treatment were noted as well.

The primary outcome measure in this study was VAS score and 24 h analgesia requirements. The second outcome measures were complications and/or side effects related to analgesia treatment.

Statistical analysis was performed with the statistical package of social science, SPSS program. Categorical variables were expressed as number (percentage) and continuous variables as mean ± standard deviation. P values <0.05 were considered to be statistically significant.

Results

During the study period, 24 patients were enrolled in the study. One patient was excluded from the analysis due to acute kidney rejection and one patient had accidental catheter removal. He was also excluded from the analysis. Out of 22 patients, group E (where combined epidural analgesia and general anesthesia was used) included 11 patients (50%), and group G (where general anesthesia and i.v. analgesia was used) also included 11 patients (50%) (Figure 1). None of group E patients received any other kind of regional anesthesia except epidural. Three patients in G group had required rescue analgesia in the end of the surgery. There was no significant difference in demographic profile and clinical data of patients between both groups. Only two patients from group E and one patient from group G did not undergo regular scheduled dialysis (Table 1).

Table 1. Demographic and clinical profile

Demographic and clinical data	Group E [n=11]	Group G [n=11]
Age [years] mean±SD	40.54±16.5	37.63±15.22
Female/Male	3/8	2/9
ASA II/III	2/9	1/9
Duration of surgery [minutes] mean±SD	201±26	203±31

*ASA- American society of Anesthesiologists; n = number of patients; SD-Standard deviation

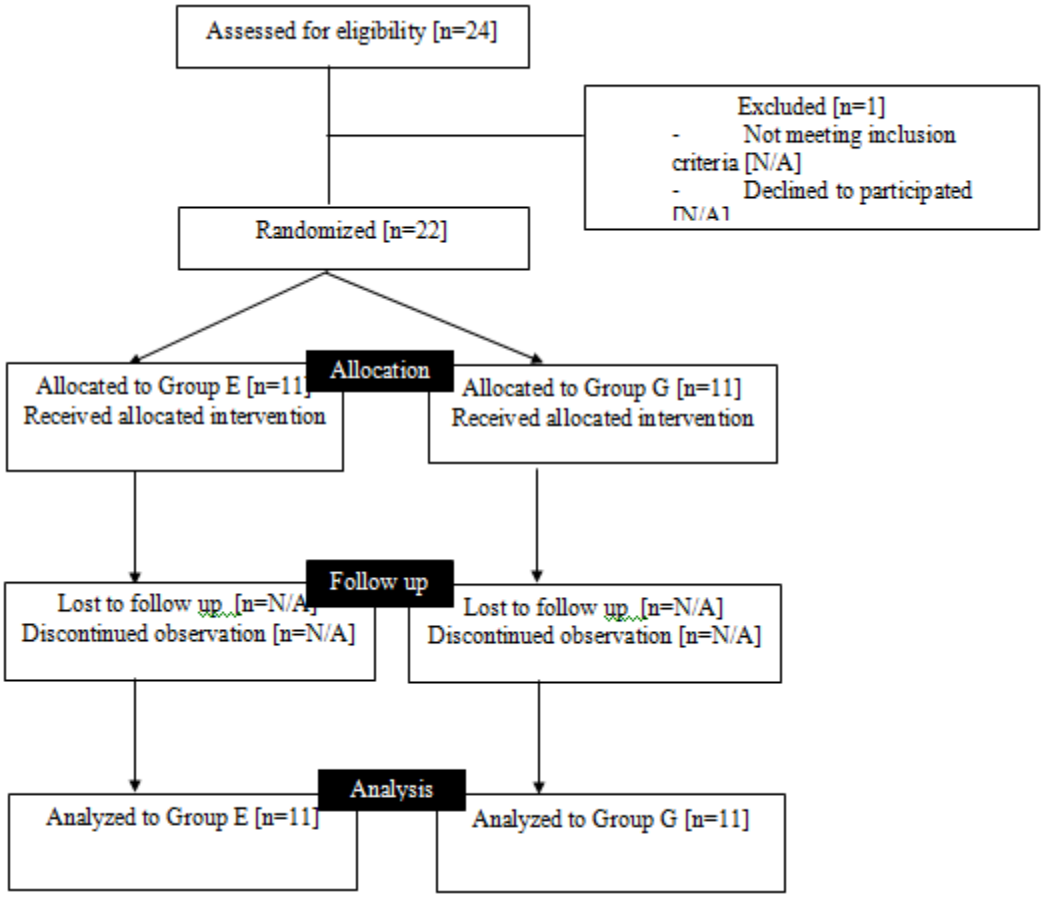

Fig. 1. Consolidated standards of reporting trials flow diagram

Table 2. Postoperative analgesic requirements in first 24h

Analgesia management	Group E (n=11)	Group G (n=11)
TFAR (minutes) mean±SD	35±24.15	15±12.12
EPDK total continuous infusion (h)	14±8.9	/
Nº of patients received opioid analgesics	/	4
Nº of patients received NSAID	1	/
Nº of patients received Paracetamol	1	11

*TFAR – Time to first analgesia requirements; n = number of patients; EPDK – epidural catheter; NSAID – non-steroidal anti-inflammatory drug

Group E had lower VAS pain score both at rest and on movement but only in the first 2 h (VAS at rest E. 3.1±0.3 vs. G. 4.0±0.3, VAS on movement E. 4.2±0.6 vs. G. 4.5±0.3) ($p<0.05$). The pain score by VAS scale did not differ between groups at 6 h, 12 h and 24 h postoperatively (p=NS) (Table 2, Table 3, Table 4, Figure 2, Figure 3).

Table 3. Visual analog scores (VAS) on rest

Time (h)	Group E (n=11)	Group G (n=11)	P value
2h	3.1 ± 0.3	4.0 ± 0.3	P < 0.005
6h	2.7 ± 0.4	2.9 ± 0.5	P = NS
12h	2.1 ± 0.6	2.0 ± 0.6	P = NS
24h	1.9 ± 0.1	1.9 ± 0.4	P = NS

*n = number of patients; p = significance between the groups; NS = non-significant

Table 4. Visual analog scores (VAS) on movement

Time (h)	Group E (n=11)	Group G (n=11)	P value
2h	4.2±0.6	5.1±0.3	P < 0.005
6h	3.1±0.1	3.0±0.3	P = NS
12h	2.9±0.5	3.1±0.6	P = NS
24h	2.4±0.2	2.6±0.4	P = NS

*n = number of patients; p = significance between the groups; NS = non-significant

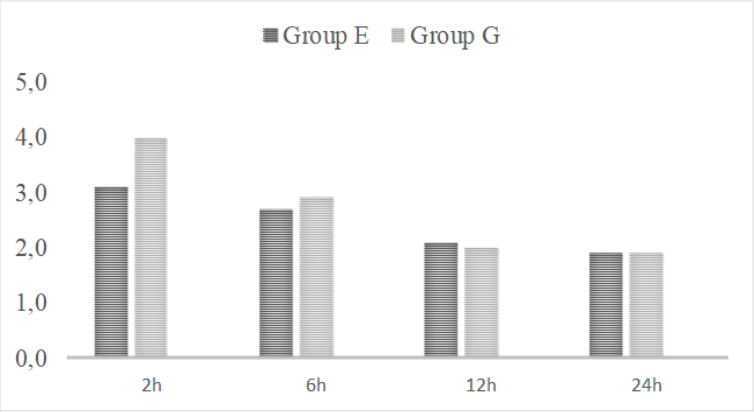

Fig. 2. Graph depicting VAS at rest

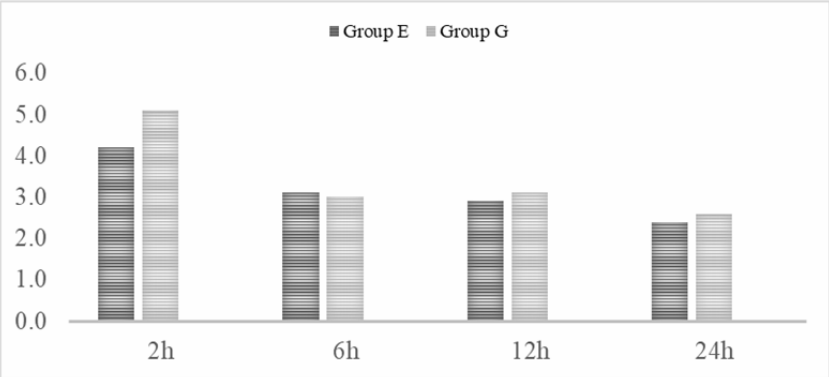

Fig. 3. Graph depicting VAS at movement

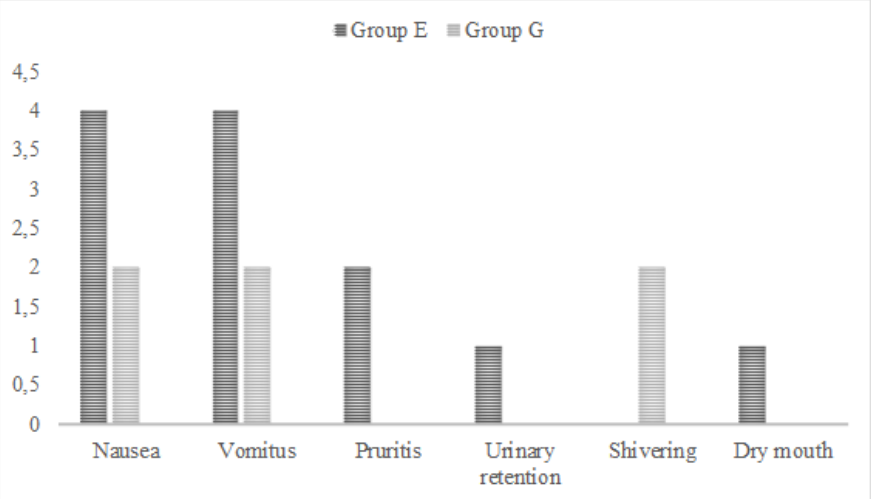

Fig. 4. Incidence of side effects in the Groups E and G

The evaluation of complications and side effects showed the highest incidence in E group. Except from accidental catheter removal in one patient, who was excluded from the analysis, there was catheter blockage in another patient. Due to hemorrhage in the surrounding tissue, the epidural catheter was preliminary removed on the second postoperative day after evaluation was finished. However, the patient had no need of it anymore. Nausea, vomiting and pruritus were reported most often. Even 4 patients felt nausea and vomiting, and 2 patients complained of pruritus. One patient complained of urinary retention and one of dry mouth. No other complication or side effects such as respiratory depression was noticed. On the other hand, in-group G, two out of four patients who received rescue analgesia with opioids had nausea and vomiting. Two patients reported shivering and there was no report of any other complication or side effects in group G (Figure 4).

Discussion

It is difficult to quantify/assess the contribution of good analgesia in good outcome of kidney transplant recipients. Not satisfactory analgesia, fear of possible graft rejection, anxiety and stress increase the risk of a significant postoperative pain in kidney transplant recipients. However, the management of analgesia should not compromise the graft function [8-10]. The results of our study indicated that epidural analgesia and i.v. analgesic drugs are used commonly among anesthesiologists in our institution. On the other hand, other regional anesthesia techniques are not a preferred choice and none of our patients received other kind of regional technique except epidural. On the contrary, there are many reports in the literature regarding the use of regional analgesia techniques for kidney transplant recipients. The most often used is transversus abdominis plain block. Currently no superior recommendation of transversus abdominis plain block over a combined general and epidural or general anesthesia exists [7, 11,12]. In our evaluation, only one patient received NSAID. Knowing the toxicity of NSAIDS there should be always a suspicion in their use, especially if edema, hypertension, decreased GFR or increased metabolism degradation products (creatinine and urea) exist [13]. The choice for analgesia management depends on the characteristics including hemodynamically stability, minimal blood loss intraoperative, early mobilization, satisfactory analgesia, and lower incidence of side effects and complications [14]. The side effects in both groups were different. In group E a larger number of patients suffered from side effects and had complications (72%) compared to group G (18%), where two patients who were shivering, received an additional opioid analgesic (tramadol) and despite the use of ondansetron had nausea and vomiting. Similar results were presented in the randomized study of Bajwa *et al*. where epidural versus general anesthesia was compared for renal surgeries [15]. Likewise, there is no stronger evidence that support the use of opioids over other drugs in kidney impairment due to potent active metabolites negative feedback. Epidural analgesia is reported to be effective and without significant complications in a limited series [16]. The combination of local epidural anesthetic and opioids has been shown to provide reduction in postoperative pulmonary complications following major abdominal surgeries [17]. Theoretically risks of epidural catheter analgesia in kidney transplant patients results from the common coagulation disorders (platelet dysfunction predominately), cardiovascular comorbidities, fluid shifts and hypotension and reduced graft perfusion. Many patients are requiring postoperative supportive anticoagulant drugs for optimizing graft survival and patients with cadaveric kidney transplant who may suffer from acute tubular necrosis often need post-transplant dialysis due to good long-term outcome and require heparinisation [5,18]. In our observation, one patient had hemorrhage in the surrounding area of the catheter and it was removed on the second postoperative day. Results from our analysis showed a statistical significance in attaining analgesia for the first 2 h in favor of E group. With reference to the other time intervals, no statistical significance was noticed between the groups measured by VAS scale. Patients had satisfactory analgesia at rest and on movement. Similar results have been reported in the literature and there is no consensus proposing one method over another [4,5,15]. One recently published study has reported benefits for graft function in the kidney donor patients who received epidural analgesia. However, the recipients received only general anesthesia and the study had many limitations [19]. Morkane *et al*. stated that the use of paracetamol as an acute painkiller should not be forbidden [5]. Our study results showed that paracetamol was a drug of choice for our anesthesiologist. It provided good analgesia and was safe to be used except in patients who have liver dysfunction. Only four patients from G group required an additional opioid analgesia drug. It is important to say that most of the group G patients received only one dose of medication for the period of 24 h. In-group E, except in one patient, continuous infusion on epidural catheter was discontinued before 24 h and the patient did not ask for additional analgesia. We assume that this was due to the narrow incision in lower abdomen and superficial placement of the transplanted kidney. Therefore, a question should be addressed; is invasive neuraxial epidural analgesia necessary in patients with end stage kidney disease who underwent kidney transplant surgery? Debates over perioperative and postoperative pain management are evident in continental Europe, with ongoing discussion and investigation [20].

This study has a number of limitations that could be applied to future research. First, because this is a single-center study, generalizability is limited. The sample was not randomized, and analgesia was managed according to the anesthesiologist in charge preferences. There is also lack of long postoperative follow-up to evaluate whether there are other late-onset complications. Number of investigated subjects is low.

Conclusion

The study highlighted the variety in clinical practice regarding anesthesiologist preferences for pain management in kidney transplant recipients. This evaluation did not show any difference between anesthetic techniques and clinical results. However, probably epidural analgesia is probably not preferred choice due to invasiveness in the overall low pain intensity.

Kidney transplant recipients are a non-homogenous group of patients with different medical pre-transplant

health history and multiple comorbidities. Therefore, personalized anesthetic technique approach is recommended.

Conflict of interest statement. None declared.

References

1. Gavrilovska Brzanov A, Grabner C, Mojsova Mijovska M, *et al.* Comparison of anesthesia management for kidney transplant-through case report. *Physioacta* 2019; 13(1): 119-123.
2. Mojsova Mijovska M, Gavrilovska A, Srceva Jovanovski M, *et al*. The Influence of Targeting Central Venous Pressure on Early Graft Function after Living Donor Kidney Transplantation. *J Anesth Surg* 2017; 4(1): 32-35.
3. Spasovski G, Dohcev S, Stankov O, *et al.* The improvement in kidney transplant program in R. Macedonia-what are the clues? *Prilozi* 2013; 34: 9-13.
4. Hadimioglu Z, Ertug Z, Bigat M, Yilmaz A. A Randomized Study Comparing Combined Spinal Epidural or General Anesthesia for Renal Transplant Surgery. *Transplant Proc* 2005; 37(5): 2020-2022.
5. Morkane MC, Fabes J, Banga N, *et al*. Perioperative management of adult cadaveric and live donor renal transplantation in the UK: a survey of national practice. *Clin Kidney J* 2019; 12(6): 880-887.
6. Pearse RM, Moreno RP, Bauer P, *et al*. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; 380: 1059-1065.
7. Kloesel B, Vlassakov KV. Regional Analgesia Techniques for Adult Patients Undergoing Solid Organ Transplantation. *Curr Anesthesiol Rep* 2018; 8: 217-224.
8. Waits SA, Hilliard P, Sheetz KH, *et al*. Building the case for enhanced recovery protocols in living kidney donors. *Transplantation* 2015; 99(2): 405-408.
9. Oliveira B, Mascarenhas C, Cardoso G, *et al*. Assessment of the degree of satisfaction among living kidney donors. *Transplant Proc* 2011; 43(1): 43-47.
10. Peters TG, Repper SM, Vincent MC, *et al*. One hundred consecutive living kidney donors: modern issues and outcomes. *Clin Transpl* 2002; 16(Suppl 7): 62-68.
11. Parikh BK, Waghmare V, Shah VR, *et al*. The analgesic efficacy of continuous transversus abdominis plane block in renal transplant recipients. *J Anaesthesiol Clin Pharmacol* 2015; 31(4): 531-534.
12. Soltani Mohammadi S, Dabir A, Shoeibi G. Efficacy of transversus abdominis plane block for acute postoperative pain relief in kidney recipients: a double-blinded clinical trial. *Pain Med* 2014; 15(3): 460-464.
13. Mulka-Gierek M, Foroncewicz B, Paczek L, *et al*. NSAIDs, analgesics, and transplantation. *Ann Transplant* 2018; 23: 153-159.
14. Gulur P, Nishimori M, Ballantyne JC. Regional anaesthesia versus general anaesthesia, morbidity and mortality. *Best Pract Res Clin Anaesthesiol* 2006; 20: 249-263.
15. Bajwa SJ, Kaur J, Singh A. A comparative evaluation of epidural and general anaesthetic technique for renal surgeries: A randomised prospective study. *Indian J Anaesth* 2014; 58: 410-415.
16. Solonynko I, Loba M, Orel J, *et al*. Renal transplantation-choice of anaesthesia. *Wiad-Lek* 1997; 50: 1447-1448.
17. Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. *Br J Anaesth* 2001; 87: 62-72.
18. Pluta J, Nicinska B, Grzeszczyk M, *et al*. Assessment of the hemostatic parameters and platelet function on Thrombo-elastometry and impedance Aggregometry in hemodialysis patients qualified for kidney transplantation: preliminary report. *Transplant Proc* 2016; 48: 1431-1434.
19. Baar W, Goebel U, Buerkle H, *et al.* Lower rate of delayed graft function is observed when epidural analgesia for living donor nephrectomy is administered. *BMC Anesthesiology* 2019;1 9: 38.
20. Breda A, Budde K, Figueiredo A, *et al*. European Association of Urology. EAU Guidelines on Renal Transplantation, 2017; https://uroweb.org/wp-content/uploads/Renal-Transplantation-2017-pocket.pdf [August 2021, date last accessed].