When their first antimuscarinic has failed, why not take a different path?

astellas

Prescribing another antimuscarinic may be of minimal benefit after the first has failed.[1] So why not choose another route? BETMIGA is in a different class, relaxing the bladder via β_3-adrenoceptors.[2] It can be just as effective as an antimuscarinic, but it doesn't have the same side-effect profile.[3]

BETMIGA is indicated for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.[2]

Prescribing information: BETMIGA™ (mirabegron)

For full prescribing information, refer to the Summary of Product Characteristics (SPC)

Presentation: BETMIGA prolonged-release tablets containing 25 mg or 50 mg mirabegron.

Indication: Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Posology and administration: The recommended dose is 50 mg orally once daily in adults (including elderly patients). Mirabegron should not be used in paediatrics. A reduced dose of 25 mg once daily is recommended for special populations (please see the full SPC for information on special populations). The tablet should be taken with liquids, swallowed whole and is not to be chewed, divided, or crushed. The tablet may be taken with or without food.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg.

Warnings and Precautions: Renal impairment: BETMIGA has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2); based on a pharmacokinetic study (see section 5.2 of the SPC) a dose reduction to 25 mg is recommended in this population. This medicinal product is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) concomitantly receiving strong CYP3A inhibitors (see section 4.5 of the SPC). Hepatic impairment: BETMIGA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. This medicinal product is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors (see section 4.5 of the SPC). Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with mirabegron, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg). Patients with congenital or acquired QT prolongation: BETMIGA, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies (see section 5.1 of the SPC). However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medicinal products for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medicinal products for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with BETMIGA; however, BETMIGA should be administered with caution to patients with clinically significant BOO. BETMIGA should also be administered with caution to patients taking antimuscarinic medicinal products for the treatment of OAB.

Interactions: Caution is advised if mirabegron is co-administered with medicinal products with a narrow therapeutic index and significantly metabolised by CYP2D6. Caution is also advised if mirabegron is co-administered with CYP2D6 substrates that are individually dose titrated. In patients with mild to moderate renal impairment or mild hepatic impairment, concomitantly receiving strong CYP3A inhibitors, the recommended dose is 25 mg once daily. For patients who are initiating a combination of mirabegron and digoxin (P-gp substrate), the lowest dose for digoxin should be prescribed initially (see the SPC for full prescribing information). The potential for inhibition of P-gp by mirabegron should be considered when BETMIGA is combined with sensitive P-gp substrates. Increases in mirabegron exposure due to drug-drug interactions may be associated with increases in pulse rate.

Pregnancy and lactation: BETMIGA is not recommended in women of childbearing potential not using contraception. This medicinal product is not recommended during pregnancy. BETMIGA should not be administered during breast-feeding.

Undesirable effects: Summary of the safety profile: The safety of BETMIGA was evaluated in 8433 patients with OAB, of which 5648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received BETMIGA for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with this medicinal product, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with BETMIGA 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving BETMIGA 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving BETMIGA 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving BETMIGA 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving BETMIGA 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. Adverse reactions: The following list reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be established from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The adverse events are grouped by MedDRA system organ class. *Infections and infestations:* Common: Urinary tract infection, Uncommon: Vaginal infection, Cystitis. *Psychiatric disorders:* Not known (cannot be estimated from the available data): Insomnia*, Confusional state*. *Nervous system disorders:* Common: Headache*, Dizziness*. *Eye disorders:* Rare: Eyelid oedema. *Cardiac disorders:* Common: Tachycardia, Uncommon: Palpitation, Atrial fibrillation. *Vascular disorders:* Very rare: Hypertensive crisis*. *Gastrointestinal disorders:* Common: Nausea*, Constipation*, Diarrhoea*, Uncommon: Dyspepsia, Gastritis, Rare: Lip oedema. *Skin and subcutaneous tissue disorders:* Uncommon: Urticaria, Rash, Rash macular, Rash papular, Pruritus, Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. *Musculoskeletal and connective tissue disorders:* Uncommon: Joint swelling. *Renal and urinary disorders:* Rare: Urinary retention*. *Reproductive system and breast disorders:* Uncommon: Vulvovaginal pruritus. *Investigations:* Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. * signifies adverse reactions observed during post-marketing experience. Prescribers should consult the SPC in relation to other adverse reactions.

Overdose: Treatment for overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure, and ECG monitoring is recommended.

Basic NHS Cost: BETMIGA 50 mg x 30 = £29, BETMIGA 25 mg x 30 tablets = £29

Legal classification: POM

Marketing Authorisation number(s): EU/1/12/809/001 – 018

Marketing Authorisation Holder: Astellas Pharma Europe B.V. Sylviusweg 62. 2333 BE Leiden. The Netherlands.

Date of Preparation of Prescribing information: June 2019

Job bag number: BET_2019_0023_UK

Further information available from: Astellas Pharma Ltd, Medical Information: 0800 783 5018. For full prescribing information, please see the Summary of Product Characteristics, which may be found at www.medicines.org.uk

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018

October 2020

References: 1. Chancellor MB et al. Int Urol Nephrol 2016;48:1029–36. **2.** BETMIGA Summary of Product Characteristics. **3.** Maman K et al. Eur Urol 2014; 65: 755–65.

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Original Article

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Robot-assisted kidney transplantation: update from the European Robotic Urology Section (ERUS) series

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Objective

To report the results of the robot-assisted kidney transplantation (RAKT) experience performed in 10 European centres by members of the European Robotic Urology Section (ERUS)-RAKT group.

Patients and Methods

This is a multicentre prospective observational study of RAKT. Descriptive analysis of recipients and donor characteristics, surgical data, intraoperative outcomes, complications rate and functional results were collected and analysed.

Results

Between July 2015 and September 2019, 291 living-donor RAKTs were performed. Recipients were mostly male (189 [65%]), the mean Standard deviation (SD) age was 45.2 (13.35) years, the mean (SD) body mass index was 27.13 (19.28) kg/m^2, and RAKT was pre-emptive in 155 (53.8%) cases. Right and multiple arteries kidneys were used in 15.4%. The mean (SD) total surgical and re-warming time was 244 (70.5) min and 53.16 (15.27) min, respectively. In all, 17 patients presented with postoperative bleeding (5.7%). Five kidneys had delayed graft function; five (2%) were lost due to thrombosis and one due to acute rejection. Two patients had arterial stenosis, three had incisional hernias, six had ureteric stenosis, and nine had lymphoceles. Neither surgical nor re-warming times were correlated with postoperative serum creatinine levels ($P > 0.05$). Comparison of surgical data between the first 120 cases and the following 171 cases showed a significantly shorter total surgical time in the second group (265 vs 230 min, $P = 0.005$).

Conclusions

This is the largest European multicentre study of RAKT with good surgical and functional results competitive with open kidney transplant series, with a relatively short learning curve when performed in centres with a wide experience in open kidney transplantation and robotic surgery.

Keywords

kidney transplantation, robotics, minimal invasive surgery, living donor, robot-assisted kidney transplantation, #KidneyTransplant

Introduction

Over the last 20 years, surgery has experienced a revolution towards minimally invasive surgery. This revolution was not seen in the field of kidney transplantation, probably due to the challenges of performing vascular anastomosis using laparoscopic instruments and two-dimensional vision. The introduction of robotics has filled the gap, enabling the intracorporeal vascular anastomosis required for kidney transplantation.

In this specific population that is usually fragile and under immunosuppressive treatment, minimally invasive surgery may be beneficial. A recent systematic review comparing open vs minimally invasive operative recipient techniques showed, although with low level of evidence that minimally invasive techniques resulted in lower infection and incisional hernia rates, improved cosmetic result and postoperative recovery. Disadvantages included prolonged cold ischaemia time, re-warming time, and total operation time [1].

The first report on robot-assisted kidney transplantation (RAKT) in 2002 by Hoznek *et al.* [2], demonstrated the feasibility of vascular anastomosis in a kidney transplant using an open approach but assisted by a robot. Then 8 years later, Giulianotti *et al.* [3] and Boggi *et al.* [4], published their firsts pure RAKTs performed in the USA and Europe, respectively. After this first experience, Menon *et al.* [5,6] standardised the transperitoneal approach with hypothermia maintenance during the re-warming time. Initial data demonstrated the safety and feasibility of the procedure.

In 2013, the first publication on RAKT in 39 obese patients, with a mean body mass index (BMI) of 42.6 kg/m^2, showed good results [7]. Then 2 years later, during the summer of 2015, three European centres performed a pure RAKT [8–10]. Since then, this technique has been increasingly used worldwide, and especially in many European centres. At the same time, the extraperitoneal approach for RAKT has been introduced by Tsai *et al.* [11], with promising results.

With the introduction of robotics in kidney transplantation surgery, the European Association of Urology Robotic Urology Section (ERUS) has created a RAKT group with the aim of developing a common database to improve analysis of the results and confirm the feasibility and safety of this new procedure. To date, 10 centres have joined the group and currently >300 RAKTs have been performed.

The aim of our present study was to report the surgical results, complications rate and functional graft outcomes of the ERUS-RAKT series.

Patients and Methods

Patients and Dataset

This is a multicentre prospective observational study of RAKT performed by members of the ERUS-RAKT group, created in 2015. A specific web-based dataset was created to prospectively collect data on patients undergoing RAKT [12]. This dataset follows protection of personal data through a patient identity codification. Every centre has its own user identification and password. Currently, the group is consists of 10 centres across Europe with previous wide experience in open kidney transplantation and robotic surgery.

Variables collected into the database include: sociodemographic data, surgical and functional outcomes, early (30-day) postoperative complications, and 90-day re-admission rate. Warm ischaemia time represents the time between clamping artery in the donor and *ex vivo* perfusion, and re-warming time is defined as the time between graft insertion in the abdominal cavity until re-vascularisation.

In this study, we analysed the data from RAKT recipients prospectively collected into the multi-institutional ERUS-RAKT common database between July 2015 and September 2019, after Ethics Committee approval and patient informed consent.

We also compared the surgical results between the first 120 cases and the subsequent cases.

Surgical Technique

The surgical technique for RAKT followed the principles of the Vattikuti-Medanta technique, using a transperitoneal approach with minimal inter-centre variations [4,5].

A multidisciplinary team before surgery assessed donors and recipients. A CT angiography was performed for both donors and recipients to optimise the surgical strategy and approach. Neither right kidney nor multiple donor vessels were a contraindication for kidney donation. Thanks to the growing experience with RAKT, an increasing number of recipients are eligible for this technique. Currently, there are no guidelines on RAKT indications, but our group's experience decided that absolute contraindications for RAKT recipients are iliac artery atherosclerosis and prior bilateral kidney transplantation.

Statistical Analysis

Variables recorded in the common database were exported in a Statistical Package for the Social Sciences (SPSS®) database to perform statistical analysis. Statistical analysis was performed using SPSS, version 23 (IBM SPSS 140 Statistics for Mac, Armonk, NY, IBM Corp). All tests were two-sided

with a significance level set at $P < 0.05$. Descriptive statistics were obtained reporting means and standard deviations (SDs) for continuous variables, and frequencies and proportions for categorical variables, as appropriate. Comparison of surgical times between the first series reported and subsequent cases was done using the Student's *t*-test.

Results

A total of 291 living-donor RAKTs were analysed. In most cases the donor nephrectomy was performed using conventional laparoscopy; in 16 (5.5%) cases, a laparoscopic-assisted transvaginal approach was used (Barcelona and Toulouse); in 42 (14.4%) cases, the donor nephrectomy was performed robotically (Ghent, Florence and Saarland). All centres used organ solution preservation such as Celsior (IMTX Sangstat, Lyon, France), Institut Georges Lopez 1 (IGL1; Institut Georges Lopez, Lissieu, France) and Custodiol l (Koehler Chemie, Alsbach-Haenlein, Germany).

Donor and recipient characteristics are listed in Table 1. In our series, 51 (17.5%) cases in the living-donor group were ABO-incompatible. The desensitisation protocol consisted of rituximab, plasma exchange or immune-adsorption, and immunoglobulins. Around half of recipients were in a pre-emptive condition.

As mentioned before, all cases were performed using the previously described technique [5,6], a transperitoneal approach with minimal variations. The graft was introduced into the abdomen through an umbilical incision in 238 cases (81.7%) or Pfannenstiel incision in 48 cases (16.5%), using a GELPOINT® (Applied Medical, Rancho Santa Margarita, CA, USA) device. In five cases the vagina was used as a natural orifice for graft introduction. In case of an iliac vascular abnormality or occupied iliac fossa for previous kidney transplant, the donor kidney was transplanted in the left iliac fossa (18 cases [6.2%]). In three cases, the iliac vein was transposed to facilitate venous anastomosis and in one case an end-to-end ureter anastomosis was made using the recipient ureter because of the poor vascular condition of the donor ureter.

The surgical data are summarised in Table 2, with special attention to surgical complications (Tables 4 and 5). In all, 45 (15.4%) cases had multiple arteries (three arteries in four cases) that required bench reconstruction in some cases before implantation and 44 (15.4%) cases of right donor kidneys.

Eight cases (2.7%), from different centres and at the beginning of the series, required immediate conversion to open surgery because of bleeding (three cases) or bad perfusion of the kidney detected intraoperatively (five cases). One case required re-perfusion and re-anastomosis; the others recovered perfusion spontaneously.

There were early (30-day) complications in 54 (18.5%) cases. The most frequent complication was postoperative bleeding, seen in 17 (5.8%) cases. Six patients required blood transfusion, six required surgical revision to evacuate the haematoma, and two needed selective embolisation for active bleeding (from a capsular renal artery and a hypogastric artery). The remaining three patients were observed.

Six (2%) kidneys were lost due to arterial thrombosis (two cases), venous thrombosis (three cases), and acute rejection (one case) during the first week; all were treated by transplantectomy and none of the kidneys were torsed. This complication occurred at different centres and during the first cases. During follow-up, 13 more cases developed some grade of graft rejection, which was treated with specific medical treatment with a good end result. During the immediate postoperative period six (2%) patients developed paralytic ileus, in two cases surgical exploration was required without any abnormal findings. During the first 30-day period only one wound infection was reported.

Functional outcomes were assessed by serum creatinine and estimated GFR (eGFR). Figure 1A,B reflect serum creatinine levels and eGFR of recipients, showing a progressive improvement in renal function. Delayed graft function (DGF), considered as the need for dialysis during the first week after transplantation, was seen in five patients (1.7%); all of them reported in the dialysis group of patients. Table 3

Table 1 Patient and living-donor characteristics ($n = 291$).

Variable	Value
Donor characteristics	
Sex, male/female, *n* (%)	97 (38)/155 (62)
Age, years, mean (SD)	50.8 (10.8)
BMI, kg/m^2, mean (SD)	25.5 (3.6)
Side, left/right, *n* (%)	241 (84.6)/44 (15.4)
Recipient characteristics	
Sex, male/female, *n* (%)	189 (65)/102 (35)
Pre-emptive, yes/no, *n* (%)	155 (53.8)/133 (47.2)
Age at surgery, years, mean (SD)	45.2 (13.35)
BMI, kg/m^2, mean (SD)	27.13 (19.28)
Vascular anatomy, *n* (%)	
Multiple arteries	45 (15.4)
Multiple veins	4 (1.3)

Table 2 Surgical data ($n = 291$).

Variable	Mean (SD)
Operative time, min	244.38 (70.5)
Console time, min	164.88 (56.2)
Warm ischaemia time, min	2.9 (2.2)
Re-warming time, min	53.16 (15.27)
Arterial anastomosis time, min	18.71 (6.1)
Vein anastomosis time, min	20.54 (7.2)
Uretero-vesical anastomosis time, min	23.5 (8.8)
Estimated blood loss, mL	153 (118)

Fig. 1 (**A**) Post-RAKT creatinine level and (**B**) GFR evolution.

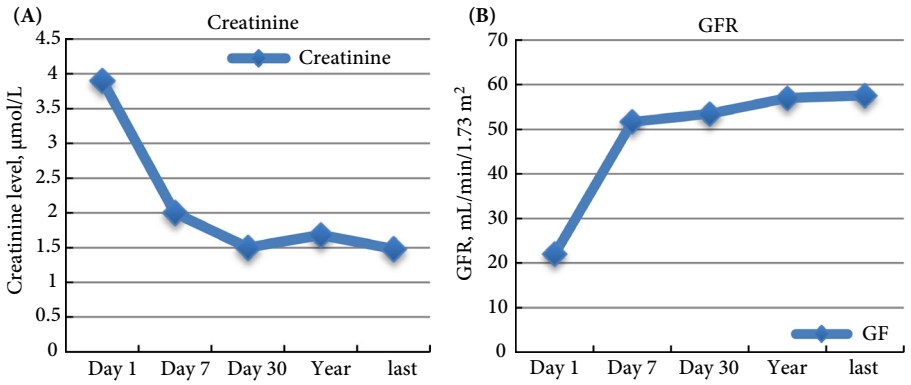

Table 3 Early complications graded according the Clavien–Dindo classification system.

Complication	*N* (%)
Grade I	
Wound infection	1 (0.3)
Bleeding (observation)	3 (1)
Ileus	4 (1.4)
Pyelonephritis	1 (0.3)
Grade II	
Deep venous thrombosis	1 (0.3)
Bleeding with transfusion	6 (2)
Grade IIIa	
Embolisation	2 (0.7)
DGF	5 (1.7)
Grade IIIb	
Transplantectomy for arterial thrombosis	3 (1)
Transplantectomy for vein thrombosis	3 (1)
Bleeding requiring surgical exploration	6 (2)
Ileus requiring surgical exploration	2 (0.7)
Transplantectomy for acute rejection	1 (0.3)
Grade IV	0
Grade V	0

Table 4 Late complications graded according to the Clavien–Dindo classification system.

Complication	*N* (%)
Grade I	
Lymphocele	2 (0.7)
Ureteric stenosis (conservatively)	2 (0.7)
Grade II	0
Grade IIIa	
Lymphocele	2 (0.7)
Angioplasty	1 (0.3)
Ureteric stenosis (endoscopically)	2 (0.7)
Grade IIIb	
Lymphocele	5 (1.7)
Hernia repair	3 (1)
Ureteric stenosis (re-anastomosis)	2 (0.7)
Grade IV	0
Grade V	1

lists the early complications according to the Clavien–Dindo classification.

Late complications were defined as >90 days after RAKT. After this period of time two arterial stenoses (0.6%) were diagnosed, in one case an angioplasty was carried out and the other one did not require treatment. Three patients (1%) required surgery for umbilical incisional hernia repair and six patients (2.1%) developed ureteric stenosis, two were treated conservatively, two required ureteric re-implantation, and the other two were treated endoscopically with balloon dilatation.

Nine lymphoceles (3%) were diagnosed during follow-up; five required laparoscopic marsupialisation and two were drained percutaneously. Table 4 lists the late complications according to the Clavien–Dindo classification. One patient died due to pulmonary thromboembolism at 4 months after surgery, which was not related to surgery.

Table 5 Correlation between operative time and re-warming time with creatinine.

	Operating time		Re-warming time	
	r	*P*	*r*	*P*
POD7				
Creatinine level, µmol/L	0.10	0.08	0.10	0.08
POD30				
Creatinine level, µmol/L	0.08	0.17	0.05	0.38
1 year				
Creatinine level, µmol/L	0.06	0.39	0.005	0.94

POD, postoperative day

Neither surgical time nor re-warming time showed any correlation with postoperative serum creatinine levels at 7 days, 30 days, and 1 year follow-up ($P > 0.05$; Table 5). The mean (SD) follow-up was 24.7 (12.6) months.

We compared the surgical data between the first cases previously described (July 2015–May 2017) [13] and the

Table 6 Comparison between periods for surgical times.

Time, min, mean (SD)	Initial (n = 120)	New (n = 171)	P
Total surgery	250 (80)	230 (71)	<0.005
Re-warming	50.26 (11.5)	52.5 (15.4)	0.4
Arterial anastomoses	19.26 (6.5)	18.3 (6.7)	0.2
Vein anastomoses	20.36 (6.5)	19.9 (7.5)	0.12
Uretero-vesical anastomoses	21.01 (9.6)	23.2 (8.3)	0.47

subsequent cases performed between June 2017 and September 2019. Although surgical times were shorter in the second group, only the total surgical time was significantly shorter (Table 6).

Discussion

Kidney transplantation is the treatment of choice for patients with end-stage renal disease because of improved survival and quality of life compared with dialysis [13]. The application of minimally invasive techniques, such as laparoscopy and robotic surgery, offers the possibility of reducing the morbidity in these immunocompromised patients by obtaining faster recovery periods, reduced wound infections, and better cosmetic results. This benefit should be even greater for obese patients, in whom a larger incision is required for kidney transplant surgery.

Following the first European experience and after consolidation by the ERUS-RAKT group [12–14], RAKT has experienced a substantial expansion in many centres in Europe and around the world, with our group performing >300 cases in the last 4 years. The construction of a unique prospective online database has permitted the analysis of more cases. Our present series is characterised by the use of the same transabdominal technique with minimal centre variations and mainly from living donors.

Consistent with the first published results [12], the present study confirms that expert surgeons in robotics and kidney transplantation can perform RAKT safely. Cadaveric RAKT courses and mentor's assistance during the first cases can reduce the learning curve. The RAKT group has permitted a forum for doubts and improvements, obtaining better results over time.

Regarding donor and recipient characteristics, we have noticed an increasing number of kidneys with multiple vessels and recipients with previous kidney transplantation. In the present analysis, there were 45 kidneys with multiple arteries compared to seven patients in the first report. We noticed an exponential increase in the number of cases with complex vascular anatomy in the last 100 cases. A more detailed description of the first 21 cases of multiple arteries kidneys from our group has recently been published and the final conclusion is that surgical and functional results using those grafts were the same as using simple vessel grafts, with a similar complication rate [15]. Right kidneys were used at the same percentage in both periods (15%); this probably reflects the previous wide experience in laparoscopic living-donor kidney transplantation in all the centres. In the literature, initial experience with laparoscopically harvested right kidneys was characterised by more renal vein thrombosis [16]. Nonetheless, recent studies have shown similar results using left or right kidneys [17,18]. In two cases an iliac vein transposition was carried out to facilitate venous anastomosis in right kidneys. Ciudin *et al.* [19] described this technique in 2012, which allows for a reduction in the space between vein anastomosis. At that time, 43 right laparoscopic living-donor kidneys were transplanted using this technique. Neither vein thrombosis nor lymphoceles were seen.

If we take a look at surgical times, the new cases were less time consuming, becoming competitive with open procedures. There was a statistically significant difference between the first 120 cases and the following 171 cases in operative time, confirming improvement over time. We noticed a reduction in operative time during this second period, even taking into account the new centres with few cases. This was probably achieved thanks to the transmission of knowledge within the RAKT working group.

During this period other European centres performed RAKT using an extraperitoneal approach. Michiels *et al.* [20] in 2017 reported the first European case using this approach. The authors concluded that using this approach might minimise difficulties encountered in obese patients with a potentially difficult dissection of the pelvic vessels, because the bowel is contained by the peritoneum, reducing possible complications. More recently the group of Bruyère *et al.* [21] published eight cases using the extraperitoneal approach with a 4-cm incision in the iliac fossa to place the Alexis port for kidney introduction. The median hospital stay was 14 days. They described one conversion for bleeding; a laparotomy for bowel injury suspicion and two patients had DGF.

The outcomes of our present RAKT series are promising and consistent with other RAKT series [4–21] and should be considered as an alternative to the open approach in urological centres with experience in robotic surgery and kidney transplantation. Six kidneys were lost due to arterial or venous thrombosis during the first cases in different centres, probably related to the technical mistakes early in the learning curve. All these patients required transplantectomy.

A typical complication in kidney transplantation is lymphocele formation due to iliac vessel dissection. In our present series, only 3% of patients developed this complication and active treatment was required in seven cases. This low percentage could be explained by the transperitoneal approach, which allows natural lymph drainage to the peritoneal cavity.

Animal studies demonstrated a reduction in renal perfusion caused by pneumoperitoneum in laparoscopic living-donor nephrectomies without repercussion on kidney function when a correct hydration of the donor was performed [22]. Likewise, RAKT could also have an incremental effect on the perfusion of these laparoscopically harvested kidneys. Usually we work at 12 mmHg, but some centres use 6–10 mmHg during RAKT to reduce the potential consequences of pneumoperitoneum on graft function and this is probably most important once the kidney is re-vascularised. The use of the AirSeal system can help to maintain a stable working environment with very low pneumoperitoneum. In our present series, five patients (1.7%) presented with DGF. This percentage is equivalent to that described by Redfield *et al.* [23], from a review of 64 024 living-donor transplantations from the United Network for Organ Sharing (UNOS) dataset. In their analysis, the authors also described multiple factors (right kidney, BMI, etc) associated with DGF and the impact on graft survival. In our present series, different organ preservation fluids were used with good creatinine normalisation over time. In the present series, we could not find any possible deleterious issue of surgical time or re-warming time on kidney function measured by serum creatinine level and eGFR (Table 4).

Only eight cases (2.7%) presented with late complications: two arterial stenoses, with one treated by angioplasty; three incisional hernia repairs; and four ureteric stenoses, treated by balloon dilatation or re-implantation.

The limitations of the present study are the retrospective analysis of a prospectively collected database with some risk of detection bias and under-reporting of (low-grade) complications. This is not a single-surgeon experience; many surgeons (one or two per centre) were involved, with different backgrounds and experience. However, all surgeons had experience in both open kidney transplantation and robot-assisted urological surgery, and were trained before and performed the first cases under mentor guidance.

There could also be a selection bias, especially at the beginning of the series, where the best candidates for robotic surgery were selected: pre-emptive, without atheromatosis, first kidney transplantation, and single vessel.

Our present findings are still limited, as this is a multicentre experience coming from referral urological centres with longstanding experience in both urological robotic surgery and open kidney transplantation. However, these results encourage the maintenance of the minimally invasive procedure and even expand the indication to deceased donors and kidneys with a more complex vascular pedicle. Moreover, we are increasing the number of patients that may benefit the most from RAKT, the obese recipients. Currently, there is not a cost analysis study comparing open vs RAKT. In radical cystectomy studies, robotic procedures were shown to be more costly than open procedures, but the final cost was reduced by a lessening in the complications rate and blood loss [24]. A cost analysis study in RAKT is warranted to clarify this question.

This is the largest European multicentre study of RAKT. When performed by surgeons with previous experience in open kidney transplantation and robotic surgery the surgical and functional results are acceptable. The ERUS-RAKT working group permitted the gathering of more RAKT cases and a better knowledge transmission of this specific technique to new centres facilitating the learning curve.

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Conflict of Interest

Dr Musquera has nothing to disclose.

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Abbreviations: RAKT, robot-assisted kidney transplantation; ERUS, European Robotic Urology Section; BMI, body mass index; DCD, donors after circulatory death; eGFR, estimated GFR; DGF, delayed graft function; SD, Standard deviation.