Clinical trial results:
Efficacy of profound versus moderate neuromuscular blockade in enhancing postoperative recovery after laparoscopic donor nephrectomy - a rondomised controlled trial

Summary

EudraCT number	2016-002924-99
Trial protocol	NL
Global end of trial date	18 December 2017

Results information

Result version number	v1 (current)
This version publication date	13 February 2020
First version publication date	13 February 2020
Summary attachment (see zip file)	RELAX-1 article (RELAX-1.pdf)

Trial information

Trial identification

Sponsor protocol code	NL.58160.091.16

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02838134
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboudumc
Sponsor organisation address	Geert Grooteplein Zuid 10, Nijmegen, Netherlands, 6525 GA
Public contact	RELAX information, Radboudumc, +31 243615333, Michiel.Warle@radboudumc.nl
Scientific contact	RELAX information, Radboudumc, +31 243615333, Michiel.Warle@radboudumc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2017
Global end of trial reached?	Yes
Global end of trial date	18 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the relationship between the use of deep neuromuscular blockade (NMB) during laparoscopic donor nephrectomy (LDN) -with standard pressure pneumoperitoneum- and the early quality of recovery.

Protection of trial subjects:

In accordance to section 10, subsection 4, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

Background therapy:

induction with remifentanil, propofol and rocuronium (intubation dose 0.6 mg/kg). Anesthesia is aimed at a bispectral index score between 45-55. Tracheal intubation is performed 2 minutes after administration of 0.6 mg/kg rocuronium in both groups. In case of a BMI>30 kg/m2 the dose rocuronium will be adjusted taking into account ideal body weight.

Evidence for comparator:

Rocuronium bromide is administered intravenously (i.v.) either as a bolus injection or as a continuous infusion.
The standard intubating dose during routine anaesthesia is 0.6 mg rocuronium bromide per kg body weight, which results in adequate intubation conditions within 60 seconds in nearly all patients.

Actual start date of recruitment	01 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 96
Worldwide total number of subjects	96
EEA total number of subjects	96

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	75
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 127 living kidney donors were screened for enrolment, 18 patients refused consent, seven patients were excluded because of insufficient command of the Dutch language and one patient was excluded because of chronic use of psychotropic drugs. A total of 50 patients were allocated to profound NMB and 51 patients to moderate NMB.

Pre-assignment

Screening details:

A total of 96 patients will be randomised, based on a computer-generated list, to either deep NMB (group A) or moderate NMB (group B). Stratification by centre will be used. All adult individuals (>18 years), who are scheduled for living kidney donation are eligible for this study.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

Before the surgeons arrive at the operation room, all study medications are prepared by the anaesthesiologist or the anaesthesiologist’s assistant, after opening the envelope containing the allocation of treatment. Surgeons, scrub nurses, and research physician are blinded for group allocation. Covering of the neuromuscular monitoring equipment, nerve stimulator and computer behind sterile drapes ensures this. The attending anaesthetic staff in the operating room are not blinded as the anaesthe

Arms

Are arms mutually exclusive?	Yes
Arm title	Deep neuromuscular block/group A

Arm description:

A bolus of 0.7 mg/kg rocuronium is administered just after tracheal intubation and then an infusion of rocuronium (0.3 to 0.4 mg/kg) is started when post-tetanic count (PTC) is more than 0 and titrated towards PTC 1-2.

Arm type	Experimental
Investigational medicinal product name	Esmeron
Investigational medicinal product code	SUB10353MIG
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

A bolus of 0.7 mg/kg rocuronium is administered just after tracheal intubation and then an infusion of rocuronium (0.3 to 0.4 mg/kg) is started when post-tetanic count (PTC) is more than 0 and titrated towards PTC 1-2.

Investigational medicinal product name	Bridion
Investigational medicinal product code	SUB26695
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

After skin closure, the NMB is reversed with sugammadex using 4 mg/kg

Arm title	Moderate neuromuscular block/group B

Arm description:

No additional rocuronium is administered after tracheal intubation.

Arm type	Active comparator
Investigational medicinal product name	Esmeron
Investigational medicinal product code	SUB10353MIG
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

A bolus of 0.7 mg/kg rocuronium is administered just after tracheal intubation. no additional rocuronium is administered after tracheal intubation and the neuromuscular function was allowed to recover spontaneously.

Investigational medicinal product name	Bridion
Investigational medicinal product code	SUB26695
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

After skin closure, the NMB is reversed with sugammadex using 2 mg/kg

Number of subjects in period 1	Deep neuromuscular block/group A	Moderate neuromuscular block/group B
Started	48	48
Completed	48	48

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	96	96	
Age categorical Units: Subjects			
Adults (18-64 years)	75	75	
From 65-84 years	21	21	
85 years and over	0	0	
Age continuous			
whole group			
Units: years			
arithmetic mean	55.86		
standard deviation	± 9.830	-	
Gender categorical Units: Subjects			
Female	51	51	
Male	45	45	
Not recorded	0	0	

Subject analysis sets	
Subject analysis set title	As-treated analysis: moderate block
Subject analysis set type	Per protocol

Subject analysis set description:

In the as-treated analysis, we combined the patients with PTC 1to 3 and patients with TOF count 0 and PTC at least 4 in the profound NMB group. The five patients (10.4%) in which a TOF count 0 wasn't achieved, were analysed as moderate NMB. The two patients in the profound NMB group with missing data on their level of NMB were excluded from the as-treated analysis.

Subject analysis set title	As treated analysis - deep block
Subject analysis set type	Per protocol

Subject analysis set description:

In the as-treated analysis, we combined the patients with PTC 1to 3 and patients with TOF count 0 and PTC at least 4 in the profound NMB group. The five patients (10.4%) in which a TOF count 0 wasn't achieved, were analysed as moderate NMB. The two patients in the profound NMB group with missing data on their level of NMB were excluded from the as-treated analysis.

Reporting group values	As-treated analysis: moderate block	As treated analysis - deep block	
Number of subjects	53	41	
Age categorical Units: Subjects			
Adults (18-64 years)	41	32	
From 65-84 years	12	9	
85 years and over	0	0	

Age continuous			
whole group			
Units: years			
arithmetic mean	56.53	56.22	
standard deviation	± 9.557	± 9.671	
Gender categorical			
Units: Subjects			
Female	28	21	
Male	25	20	
Not recorded	0	0	

End points

End points reporting groups

Reporting group title	Deep neuromuscular block/group A

Reporting group description:

A bolus of 0.7 mg/kg rocuronium is administered just after tracheal intubation and then an infusion of rocuronium (0.3 to 0.4 mg/kg) is started when post-tetanic count (PTC) is more than 0 and titrated towards PTC 1-2.

Reporting group title	Moderate neuromuscular block/group B

Reporting group description:

No additional rocuronium is administered after tracheal intubation.

Subject analysis set title	As-treated analysis: moderate block
Subject analysis set type	Per protocol

Subject analysis set description:

In the as-treated analysis, we combined the patients with PTC 1to 3 and patients with TOF count 0 and PTC at least 4 in the profound NMB group. The five patients (10.4%) in which a TOF count 0 wasn't achieved, were analysed as moderate NMB. The two patients in the profound NMB group with missing data on their level of NMB were excluded from the as-treated analysis.

Subject analysis set title	As treated analysis - deep block
Subject analysis set type	Per protocol

Subject analysis set description:

In the as-treated analysis, we combined the patients with PTC 1to 3 and patients with TOF count 0 and PTC at least 4 in the profound NMB group. The five patients (10.4%) in which a TOF count 0 wasn't achieved, were analysed as moderate NMB. The two patients in the profound NMB group with missing data on their level of NMB were excluded from the as-treated analysis.

Primary: Total Score of the Quality of Recovery-40 Questionnaire (QoR-40)

End point title	Total Score of the Quality of Recovery-40 Questionnaire (QoR-40)

End point description:

The QoR-40 is a validated assessment tool for measuring a patient's self-assessed quality of recovery after surgery. It consists of 40 questions measuring 5 dimensions: patient support, comfort, emotions, physical independence and pain. Each item is rated on a scale of 1 to 5, giving a minimal score of 40 and a maximum score of 200. Higher values represent a better outcome

End point type	Primary

End point timeframe:

24 hours after detubation

End point values	Deep neuromuscular block/group A	Moderate neuromuscular block/group B	As-treated analysis: moderate block	As treated analysis - deep block
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	47[1]	47[2]	52	40
Units: Total score				
arithmetic mean (standard deviation)	169.3 (± 18.3)	169.5 (± 15.5)	168.7 (± 15.9)	171.1 (± 18.3)

Notes:

[1] - 1 patient missed one page of the QR-40 questionnaire on postoperative day 1

[2] - 1 patient did not complete the questionnaires on postoperative day 1 and 2

Attachments (see zip file)	QoR-40 questionnaire/QoR-40 questionnaire.docx

Statistical analyses

Statistical analysis title	QoR-40
Comparison groups	Deep neuromuscular block/group A v Moderate neuromuscular block/group B
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Postoperative pain

End point title	Postoperative pain
End point description: Overall maximum painscore	
End point type	Secondary
End point timeframe: Postoperative day 1	

End point values	Deep neuromuscular block/group A	Moderate neuromuscular block/group B	As-treated analysis: moderate block	As treated analysis - deep block
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	48	47[3]	52	41
Units: NRS				
arithmetic mean (standard deviation)	5.0 (± 2.3)	5.6 (± 2.1)	5.7 (± 2.1)	4.7 (± 2.3)

Notes:

[3] - 1 patient did not complete the questionaires on postoperative day 1 and 2

Attachments (see zip file)	Postoperative pain/Postoperative pain and analgesics.docx

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from admission until 60 days after surgery

Assessment type	Systematic

Dictionary used

Dictionary name	toetsingonline.nl
Dictionary version	1

Reporting groups

Reporting group title	Deep neuromuscular block/group A

Reporting group description:

A bolus of 0.7 mg/kg rocuronium is administered just after tracheal intubation and then an infusion of rocuronium (0.3 to 0.4 mg/kg) is started when post-tetanic count (PTC) is more than 0 and titrated towards PTC 1-2.

Reporting group title	Moderate neuromuscular block/group B

Reporting group description:

No additional rocuronium is administered after tracheal intubation.

Serious adverse events	Deep neuromuscular block/group A	Moderate neuromuscular block/group B	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Infection	Additional description: Readmission because of urinary tract infection		
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Deep neuromuscular block/group A	Moderate neuromuscular block/group B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 48 (18.75%)	5 / 48 (10.42%)	
General disorders and administration site conditions			
hypertension			

subjects affected / exposed	1 / 48 (2.08%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Infections and infestations			
Infection	Additional description: UTI, epididymitis, woundinfection or other		
subjects affected / exposed	8 / 48 (16.67%)	4 / 48 (8.33%)	
occurrences (all)	8	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30920983