Prospective comparative study between Deflux® and Vantris® for endoscopic treatment of vesico-ureteral reflux in children.

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Primary Objective: The treatment result expressed as the proportion of successful treatments per treatment arm (successful = VUR

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON41581

Source
ToetsingOnline

Brief title
DeVan studie

Condition

- Renal and urinary tract disorders congenital

Synonym
reflux, VUR

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: bulking agent, endosopic treatment, prospective randomised study, Vesico-ureteral reflux

Outcome measures

Primary outcome

The proportion of successful treatments per treatment arm is equal (successful = VUR <= grade 1 and/or no urinary-tract infections 6 months after the operation): Deflux® compared to Vantris®. In case it is not, it will be in favour of more success for the Vantris® treatment-arm.

Secondary outcome

• The treatment with Vantris® is cost-effective compared to treatment with Deflux®

• There is no significant difference in the number of urinary-tract infections within 6 months after the treatment in both treatment arms. In case there is, it is in favour of fewer infections in the Vantris® treatment arm.

• There is no significant difference between both treatment arms in the number of recurrences of VUR in the long term (2.5, 5 and 10 years). In case there is a difference, it is in favour of fewer recurrences in the Vantris® treatment-arm.

Study description

Background summary

Vesico-ureteral reflux (VUR) usually is a congenital defect of the vesico-ureteral junction which closes off insufficiently when the bladder fills up. As a result, urine may flow back to the kidney during bladder filling

and/or during micturition. This is in itself not harmful. However, in case of existing VUR bacteria that are in the bladder may easier emerge to the kidney, resulting in a pyelonephritis. Such pyelonephritis may be harmful as it may cause scars to the kidney resulting in a loss of kidney tissue. Antibiotic prophylaxis might decrease the infection rate in boys under one year of age and in girls.
Vesico-ureteral reflux may disappear spontaneously (maturation). Bladder dysfunction and recurrent urinary tract infections are associated with persistent VUR. It is, therefore, important that these are managed before considering a possible further (operative) treatment.
The conservative policy is continued until the child is toilet-trained. For boys the antibiotic prophylaxis is stopped than, and the boy is monitored for further urinary-tract infections. If these do not occur no further treatment will be performed and the boy is further followed yearly until after puberty for kidney growth and hypertension. Girls, who are more prone to urinary-tract infections due to the shorter urethra, are in principle always treated for VUR in case of a VUR graded higher than 2 that does not spontaneously disappear. However, there are very few studies on which treatment recommendations rely. A recent Swedish study proved that after 2 years of follow-up, antibiotic prophylaxis and endoscopic treatment decreased the infection rate and new kidney damage significantly compared to no treatment. In view of the increasing resistance to antibiotics it is however difficult to defend to prolong antibiotic treatment instead of operative treating the VUR if resolution rate is predicted to be low.
An operative correction of VUR is carried out if despite antibiotic prophylaxis children continue to have febrile urinary tract infections (pyelonephritis), or if the chance of maturation of the VUR is low. The parents* preference also plays a role: despite adequate counselling, some parents prefer an operative correction of the VUR to administering a small daily dose of antibiotics.
There are two techniques for surgical correction of VUR: endoscopically, usually applied for lower grades of VUR, or an ureteral reimplantation (an open surgical procedure). This study deals with the endoscopic procedure, which we will therefore describe in more detail.

Endoscopic treatment of VUR by means of a subosteal injection of a bulk-forming substance (usually called STNG procedure) was described for the first time in 19816 and has gained considerable popularity ever since. The technique can be applied for all grades of VUR. The operation*s success is not so much determined by the product used as by the correct position of the implants towards the ureteral orifice and the grade of VUR. Failing in the long term is usually attributed to reabsorption or otherwise disappearance of product.
When one endoscopic procedure does not resolve the VUR, a second procedure can be carried out. In case this treatment fails again and VUR is still demonstrated in a new micturition cystogram (possibly after suffering a new pyelonephritis), an open operative correction is considered the next step. A third subosteal injection of a substance is generally not deemed useful in view of the low success rate of a third attempt.

In The Netherlands most centres use Deflux® as the bulk-forming substance. As a result of its success and effective marketing, this product has virtually obtained a monopoly position on the Dutch market. Internationally and in only a few centres in The Netherlands Macroplastique® is also used. As the latter product causes a more significant tissue reaction it is not very popular.
The control of the successfulness of a STING procedure is traditionally performed by means of a micturition cystogram. This is an invasive X-ray examination involving the insertion of a bladder catheter to fill the bladder with contrast medium to establish whether there is reflux or not.
In children with low grade reflux antibiotic prophylaxis is stopped 2 to 6 weeks after the endoscopic procedure and a MCUG not routinely performed if no UTIs occur.
Most children with persisting or relapsing VUR will present with a febrile urinary tract infection. In these cases following treatment of the UTI a MCUG will need to be performed. In higher grades of VUR (grade 4-5) a MCUG will be routinely performed following endoscopic treatment.
The ideal bulk-forming product should meet a number of requirements:
• It must be easily injectable
• It must be inert
• It must be sustainable (it should not disappear)
• It should not calcify or transmute in any way
• It must be cost-effective
• The chance to successfully treat VUR with this product should approximate an operative correction (> 95%) of VUR.
Vantris® is a new bulk-forming substance introduced in the market for the treatment of VUR. The results reported in the literature are promising but scarce. The success rate after one single injection for VUR grade III-V with this product is reported to be higher (84,4%) than after injection of other existing products (71% with Deflux® in the Swedish reflux trial).
Animal-experimental research proved that the product is sustainable and does not cause a tissue reaction. Moreover, the product is pro vial less expensive than the other substances on the Dutch market for this treatment.
So far, there is no comparative study between Vantris® and other existing products. This study*s objective is to make a comparison between Deflux® and Vantris ® regarding short term (6 months) and long term (1, 2.5, 5 and 10 yrs) efficacy (VUR disappearance and non-occurrence of infections). The Dutch paediatric urologists do not want to cross over to another product without proving its effectiveness and comparing it to the established treatment, even if this is allowed by the Dutch government without further testing (wet medische hulpmiddelen en Europese regelgeving).

Study objective

Primary Objective: The treatment result expressed as the proportion of successful treatments per treatment arm (successful = VUR <= grade 1 and/or no urinary-tract infections 6 months after the operation) does at least not show a significant difference between endoscopic procedures performed with Deflux®

compared to those performed with Vantris®. In case there is a difference, this is in favour of successful treatment with Vantris®.

Secondary Objective(s):
• The treatment with Vantris® is cost-effective compared to treatment with Deflux®
• There is no significant difference in the number of urinary-tract infections within 6 months after the treatment in both treatment arms, neither after 1, 2.5, 5 and 10 years. In case there is a significant difference, treatment with Vantris® is followed by less infections than treatment with Deflux®.
• There is no significant difference between both treatment arms in the number of proven recurrences of VUR in the long term (1, 2.5, 5 and 10 years). In case there is a significant difference, treatment with Vantris® shows less recurrences of VUR than treatment with Deflux®.

Study design

Multi-centre single blind randomized study with children affected with VUR for whom an operative endoscopic correction is the advised procedure.

Duration of the study: 12.5 years in total
• Primary completion point: 6 months after randomisation of the last patient
• Secondary completion point: 10 years after randomisation of the last patient

In conformity with the current standards the following examinations have to be performed preoperatively:
• Micturition cystogram to establish the grade of VUR
• DMSA scan to investigate presence of preoperative scarring of the kidney
• Creatinin for checking the kidney function
• Ultrasound of the kidneys to register kidney size + eventual dilation of the kidney
• Urine analysis to exclude a UTI at the time of surgery

The operative procedure will be carried out as the paediatric urologist usually does. To prevent bias, each centre describes per participating paediatric urologist which technique he or she does apply and in which circumstances he/she will opt for a particular technique (traditional STING procedure, single or double hit procedure). The paediatric urologist will disclose not to change anything in this technique or follow-up unless after consultation with the study coordinator. This disclosure is part of the protocol and will be attached as enclosure 4 to this protocol.

Postoperative follow-up procedures will be carried out as the paediatric urologist usually does. Each participating paediatric urologist will describe this follow-up procedure before the beginning of the study (enclosure 4) and he/she will state no deviation from this procedure will be performed without prior consultation. This means that some paediatric urologists will examine the

disappearance of VUR by means of a MCUG; others will refrain from this but instead monitor the child by monitoring for a possible urinary tract infection. In the existing literature there is no unequivocal idea about the procedure to be followed postoperatively5. Performing an MCUG gives certainty to parents and physician but it burdens the child. Not performing an MCUG is less of a burden to the child but may lead to unnecessary contacts with the physician due to the parents* uncertainty. As VUR in itself is not harmful but urinary-tract infections may well be, it would, in cases of a lower infection risk (lower grades of VUR, earlier history of fewer infections and little damage to the kidneys with an acceptable urination pattern) in itself be safe to wait until the parents contact the physician the moment urinary-tract infections occur. UTI*s following endoscopic treatment need to be documented by a dip stick or microscopic examination and urine culture (a clean catch midstream for a child with fever with one single micro-organism being cultured, or a catheterized urine sample in the other cases).

The long-term follow-up will take place by telephone interview by the treating paediatric urologist. If deemed necessary clinically, additional examinations can be reported in between.
DMSA is a nuclear examination and is, after endoscopic treatment of VUR, only indicated in case of recurrent febrile urinary tract infections (pyelonephritis). If no urinary-tract infections occurred, the risk of newly formed scars is negligible; this makes a DMSA scan unnecessary.

Urine microscopy and culture are not necessary and uselessly burdensome if there are no signs indicating an active UTI.
In all cases of suspicion of UTI and /or fever a urine microscopy and urine culture should be performed in order to rule out a concomitant urinary tract infection, .

Study burden and risks

Nature, extent of the burden and risks associated with participation are minimal as we compare an established treatment although with 2 different products. Both products have a CE-validation and both products will be used for the intervention they are intended for. The reason we perform this study is, that both products have not been compared to each other and that the Dutch pediatric urologists do not want to replace a product by another one (especially in children) only because it is said to be better while it is cheaper.
In case the Dutch pediatric urologists would not perform this study, they would have been imposed by the hospital purchasing divisions to use the new and cheaper product without any registration of possible effects. This would have been more of a risk as no registration of side-effects, treatment failures and so on would have taken place.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

• VUR grade II to V, established through MCUG < 1 year before surgery
• No or treated dysfunctional voiding pattern
• No or treated constipation
• No active urinary-tract infection on the day of surgery
• Child between 1 and 18 years of age
• Normal serum creatinin level

Exclusion criteria

• Recurrent residual after micturition of more than 10% of the functional bladder capacity

• Neurogenic or non-neurogenic bladder disorder or a history of intermittent catheterization
• Earlier surgery to the bladder or the ureter
• urinary-tract infection, not treated
• Obstipation, not treated
• Children of parents who, for principal or other reasons, refuse to administer antibiotic prophylaxis when the paediatric urologist or treating physician indicates this to be necessary.
• Non-compliance, proven during the progress of the case history so far
• Abnormal level of serum creatinin

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-02-2013
Enrollment:	330
Type:	Actual

Medical products/devices used

Generic name:	Deflux en Vantris
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	02-11-2012

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL40924.029.12