TYRX antibacterial envelope infection prophylaxis in spinal cord stimulation

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Abstract

Background: Spinal cord stimulation (SCS) can be used to reduce chronic pain conditions when other treatments have failed. The SCS device is powered by an implantable pulse generator (IPG) similar to that used in treating cardiovascular arrhythmias (cardiovascular implantable electronic device (CIED)). Recent studies have shown that the postoperative infection rate can be reduced by surrounding the CIED in an antibacterial envelope (TYRX).
Aim: To examine if the use of the TYRX antibacterial envelope in SCS procedures reduces the postoperative infection rate.
Method: Single center retrospective study comparing infection rates in non-TYRX recipients from 2018-2020 with patients who received a TYRX antibacterial envelope in 2020 - 2021 during their SCS operation. All new SCS IPG recipients were included and subdivided into TYRX and non-TYRX groups, revision surgeries were excluded. Infection was registered if the patient received antibiotic treatment post-operative within a follow-up period of 100 days.
Results: A total of 198 patients were included, 100 in the TYRX group and 98 in the non-TYRX group. There were no significant differences between the two groups regarding age, BMI and distribution of selected risk factors (smoking, diabetes and immunosuppression).
The overall infection rate in this study was 5.56%. The infection rate was 4% in the TYRX group and 7.14% in the non-TYRX group. Fisher's exact test revealed no significant difference between the two groups ($p=0.6$).
The 4 infected TYRX recipients were treated exclusively with per oral (PO) antibiotics. Out of the 7 infected non-TYRX patients 5 were treated with PO and intravenous (IV) antibiotics, 1 exclusively with IV antibiotics and 4 had revision surgery and 3 had their devices explanted as result of the infection.
Furthermore, the overall occurrence of infection compared with risk factors, showed a significant association with diabetes ($p=0.04$). No association was found in the occurrence of infection compared with immunosuppressant use ($p=0.331$) or cigarette smoking ($p=0.135$).
A power calculation based on the infection rates of this study suggests that 856 patients in each group will be needed to prove a significant difference in infection rate between the non-TYRX and the TYRX group.
Conclusion: The TYRX antibacterial envelope displayed a tendency to reduce infection rates, along with a tendency to reduce revision surgeries and system removals due to infections. However, to prove these findings statistically significant a much larger sample size is needed. We therefore suggest that a prospective multicenter study is composed enabling inclusion of an adequate study population for further elaboration on the findings of this study.

Resume

Baggrund: Rygmarvsstimulation (SCS) kan bruges i behandlingen af kroniske smerter, når alle andre behandlingsmodaliteter er udtømte. SCS-apparaturet får strøm via et implanterbart batteri (IPG), som ligner batteriet der benyttes i behandlingen af kardielle arytmier (cardiovascular implantable electronic device (CIED)). Ved at benytte sig af en antibakteriel membran (TYRX), har studier påvist at det er muligt at reducerer postoperative infektioner ved CIED operationer.
Mål: At undersøge om TYRX antibakterielle membran har en reducerende effekt på postoperative infektioner ved SCS operation.
Metode: Sammenligningen af infektion rater mellem patienter der har modtaget TYRX antibakterielle membran i 2020- 2021, med patienter der ikke har modtaget denne i 2018 – 2020 i et single-center retrospektivt studie. Alle patienter der modtog en ny IPG i forbindelse med SCS-procedurer er inkluderet og opdelt i en TYRX-gruppe og en non-TYRX-gruppe. Revisionsoperationer blev ekskluderet fra dette stude. Infektion blev registreret, hvis der blev administreret antibiotika postoperativt, inden for follow-up perioden på 100 dage.
Resultater: 198 patienter blev inkluderet i dette studie, 100 i TYRX-gruppen og 98 i ikke-TYRX-gruppen. Der var ingen signifikant forskel på de to grupper med hensyn til alder, BMI og fordelingen af risikofaktorer (rygning, diabetes og immunosupression).
Den overordnet infektionsrate var 5.56% i dette studie. Infektionsraten for TYRX-gruppen var 4% og 7.14% i ikke-TYRX-gruppen. Fischer's exact test kunne ikke påvise statistisk signifikant forskel imellem de to grupper (p=0.6).
De 4 TYRX modtagere med infektion kunne behandles udelukkende med per oral (PO) antibiotika. Af de 7 ikke-TYRX patienter, som var inficerede, fik 5 PO og intravenøs (IV) antibiotika, 1 fik udelukkende IV antibiotika og 4 fik revisions operation, desuden endte 3 patienter med få deres apparat eksplanteret på grund af infektionen.
Endvidere, vidste studiet en statistisk signifikant sammenhæng mellem generel infektionstendens og riskofaktoren diabetes. Der kunne ikke påvises sammenhænge mellem øvrige risikofaktorer og infektion (imunosuppressiv-behandling (p=0.331), rygning (p=0.135)).
En power beregning baseret på dette studies infektionsrater, viste at det ville være nødvendigt at inkludere 856 patienter i hver gruppe for at påvise en statistisk signifikant forskel mellem TYRX- og ikke-TYRX-gruppen.
Konklusion: TYRX antibakterielle membrane viste en tendens til at reducere infektionsrater, samt en tendens til at reducere revisions operation og system fjernelser grundet infektioner.
Dette kunne dog ikke påvises statistisk signifikant grundet en for lille populationsstørrelse.
Derfor foreslår vi at der sammensættes et prospektivt multicenter studie, der vil gøre det muligt at inkludere en tilstrækkeligt forsøgspopulation, til at bygge videre på fundene fra dette studie.

Abbreviations

CIED: Cardiac implantable electronic device
CRP: C-reactive protein
CRPS: Complex regional pain syndrome
DM: Diabetes melitus
FBSS: Fail Back Surgery syndrome
IPG: Implantable pulse generator
IV: Intravenous
Mg: Milligram
Mikg: Microgram
PO: Per oral
RCT: Randomized control trial
SA: Staphylococcus Aureus
SCS: Spinal cord stimulation
TENS: Transcutaneous electrical nerve stimulator
TYRX: TYRX™ Absorbable Antibacterial Envelope, by Medtronic

Table of content

1. Introduction

Chronic pain is a highly subjective experienced condition that necessitates medical treatment in combination with physiotherapy and psychological therapy (1,2). However, when these treatment modalities fail spinal cord stimulation (SCS) and neuromodulation may offer another opportunity for pain relief.

1.1 Spinal Cord Stimulation

SCS therapy was first described in 1967 by Shealy et al (3). The treatment is well attributed for its pain-relieving effect on various conditions such as back pain, Failed Back Surgery Syndrome (FBSS), Complex Regional Pain Syndrome (CRPS), angina pectoris, phantom limb pain, chronic pancreatitis, and the effect it can assert on non-pain related conditions including sacral stimulation for fecal incontinence (4-10).

The pain-relieving mechanism by which neuromodulation is postulated to work is related to gate control theory described by Melzack and Wall et al in 1965 (11).
Electrical impulses are transmitted through electrodes which are implanted in the epidural space near the midline of the dorsal columns, resulting in modulation of neurochemical composition and activation thresholds for signal transmission. The stimuli are delivered by an implanted pulse generator (IPG), usually located in the patient's buttocks. The stimuli are thought to alternate pain perception both from ascending and descending pathways leading to segmental and supraspinal effects. Basically, this means that the gate is "closed", for ascending pain due to touch and vibration signaling mediated through the electrical current supplied by the implanted electrode in the epidural space (12,13).
The exact mechanism by which neuromodulation functions on a cellular and neurochemical level is not fully understood and will not be discussed further in this study.

1.2 Complications

Complications related to SCS procedures span from correctable complications such as electrode migration to potentially disabling complications such as epidural hematomas and infections (12,14,15).
Infections are a serious complication, both for the patients and because it is associated with great expenditures (16). In recent years infection rates have dropped due to prophylactic antibiotics, as well as other measures. However, infections are still a major complication associated with operations, and researchers are still investigating new interventions to decrease infection rates (17).

Different risk factors are known to be associated with infections when undergoing surgery. Here among are diabetes, smoking and higher BMI (18-20). All risk factors are found among the general population and are taken into consideration when undergoing surgical procedures (21).
When oral and/or intravenous antibiotic treatment becomes insufficient in the treatment of an infection, revision surgery is often attempted to salvage the implanted devices and treat the infection. During revision surgery the infected devices are bathed in antibiotics, and there upon reimplanted, leading to further procedure expenditures (16).
Revision surgery is not always enough to salvage implanted devices and removal and discharge are then performed to eradicate the infection completely.

Recent studies have shown infection rates related to SCS procedures is 2.45%, most commonly involving infections around the IPG also known as a pocket infection. Furthermore, Staphylococcus Aureus (SA) is the most frequently associated pathogen in these infections (14,17).
The biofilm producing pathogen, SA is a common and problematic pathogen related to infection in SCS procedures. Its biofilm producing abilities render it more resistant to antibiotic treatment and relating them to persistent infections commonly leading to revision surgery or removal of device (17,22).
A relatively new way to prevent the growth of biofilm forming bacteria such as SA is the TYRX™ Absorbable Antibacterial Envelope, by Medtronic (TYRX) which offers prophylactic antibiotic intervention.

1.3 TYRX Antibacterial Envelope

TYRX is a bioabsorbable polymer, with a coating that contains minocycline and rifampicin. The antibiotics are locally released into the tissue for a minimum of 7 days. It is fully absorbed in the body after approximately 9 weeks (23,24).

TYRX envelope was first used in Cardiac implantable electronic devices (CIEDs) and is well attributed for its infection rate reducing abilities as well as its economically beneficial aspects as described in multiple studies such as; COMMAND, Vanderbilt, Sharif et al, Citadel&Centurion and WRAP-IT (25-29)

The multicenter retrospective cohort study COMMAND found infection rates below 0.5% in high-risk patients treated with a TYRX envelope, within a follow-up period of 1.9 +/- 2.4 months (25).

The Vanderbilt study compared the TYRX non-absorbable and TYRX absorbable envelopes with a control group in high-risk patients within a follow-up period of 300 days. The absorbable and non-absorbable envelopes had similar effects (26)

The Shariff et al study compared absorbable TYRX envelope treated CIED patients with a control group. Shariff et al also suggest that introducing the TYRX envelope appeared to be economically beneficial when comparing costs of infection treatment with the cost of the TYRX envelopes (27).

In the Citadel&Centurion study infections occurred in 0.4% of patients treated with the TYRX envelope, showing a significantly lower infection rate when compared with a control group with an infection rate of 2.2% within a follow-up period of 12 months (28).

The most recent study, the WRAP-IT randomized controlled trial (RCT) from 2019 by Tarakji et al, investigated TYRXs potential infection decreasing properties in a large multicenter study. The study found an infection rate of 1.2% in major infections in the control group compared with a 0.7% infection rate in the group treated with a TYRX envelope, within a follow-up period of 12 months (29).
In conclusion, the above mentioned CIED studies all found an infection rate reduction in CIEDs operations, when using the TYRX envelope.
In neuro-modulatory procedures where an IPG implant is used much similar to the CIEDs in cardiac procedures, a new TYRX envelope the TYRX™ Neuro Absorbable Antibacterial Envelope (TYRX) has been developed specifically for implanted devices in neurosurgery. It is intended to cover the IPG in SCS, Deep brain stimulation and Sacral neuromodulation (23). However, the

clinically proven infection reducing abilities of TYRX envelope in SCS operations has yet to be investigated to the knowledge of this study's authors, and therefore lack the same clinical evidence as TYRX envelope in CIED operations.

The aim of the study is to observe the infection rate after the implementation of the TYRX envelope and compare it with the previous infection rates related to SCS procedures.

2. Method

The study protocol with ID-number 2021-122 was approved by the department of Quality and Association process at Aalborg university hospital, as a single center retrospective clinical control study.

2.1 Standard procedure

At Aalborg University Hospital patients referred to SCS treatment are offered a transcutaneous electrical nerve stimulator (TENS) prior to the surgical procedure as a test to evaluate potential efficacy of a permanently implanted device. The testing period varies, and some patients who respond poorly to the TENS treatment are sometimes offered SCS intervention regardless.
First step in the SCS treatment is implantation of an electrode in the epidural space, through an epidural needle, done under local anesthesia. Through the posterior paramedian epidural space the electrode is led to the point of which the pain is suspected to be mediated, often from T8- T10 (12,30).
The electrodes consist of 8 conductor units, which can deliver electrical impulses to the spinal cord. A variety of impulse patterns are available for mediation of adequate pain relief such as "Burst" stimulation (31).

The standard SCS procedure is initiated with electrode implantation on day 1. An efficacy testing period of 5 days follows thereafter, before final implantation of the IPG on day 5.
During the testing period, the patients try out different settings for their electrodes through a remote control, enabling them to manage intensity of electrical impulses and how often during the day the device is operating
If the patient does not find a suitable setting, the staff trained in battery programming can reprogram the impulse pattern. If satisfactory efficacy is unachievable the electrodes can be revised or at times removed, and the testing period may therefore vary from the individual patient.
After a successful testing period a permanent IPG is implanted on the patient's buttocks or abdomen, in a subcutaneous pocket.
If the procedure runs complication free the patient is usually discharged from the hospital the same day or the following day after the IPG implantation procedure, and the patient becomes an outpatient. The patient is hereafter advised to take a sick leave of minimum 1 month and keep the movement of their lower back to a minimum.
Control and device testing for outpatients are offered after 3 months, 6 months, 1 year, 3 years, 5 years, and 10 years. If the patients experience complications, additional controls are added, and intervention is possible e.g., reprogramming of IPG or revision surgery.

A typical course for SCS procedures is electrode implantation on Monday and IPG implantation on Friday, with testing period in between while the patient is admitted at Aalborg University Hospital.

For all patients undergoing SCS procedures at Aalborg University Hospital a standard package of medication is prescribed, additionally to the patients' ordinary medication, which includes prophylaxis antibiotic treatment, postoperative antibiotic treatment as well as antiemetic treatment and pain releiving medication for postoperative pain. Table 1 shows the standard package as prescribed. The medication package is prescribed both for electrode implantation as well as for IPG implantation.

Table 1 – Standard Prescribed Medication Package for SCS procedures

Indication	Drug name	Administration	Dosage	Amount
Preoperative				
Antiemetic prophylaxis	Marzine	PO	25 mg	1 time
Antiemetic prophylaxis	Dexamethason	PO	4 mg	1 time
Pain prophylaxis	Methadone	PO	5 mg	1 time
Pain prophylaxis	Paracetamol	PO	1 g	1 time
During operation				
Pain prophylaxis	Phentanyl	IV	50 mikg	1 time
Infection prophylaxis	Cefuroxim	IV	1,5 g	1 time
Postoperative				
Infection prophylaxis	Dicloxacillin*	PO	1000 mg	4 times daily for 3 days
Infection prophylaxis	Cefuroxim	IV	750 mg	4 times daily for 1 day

**For penicillin allergy clindamycin is used instead*
PO = per oral. IV = intravenous. g = gram. mg = Milligram. mikg = Microgram.

The above-described protocol is the standard at the department of neurosurgery at Aalborg University Hospital and may vary from other hospitals.

2.2 Study population

The study included patients from Aalborg University Hospital, treated at the neurosurgical department during a period between 1.1.2018- 15.7.2021, with a SCS implant.
The inclusion criteria were patients with chronic non-malignant pain, treated with spinal cord stimulation and subcutaneous IPG pocket, above the age of 18 and a possibility of a 100 days follow up.
The exclusion criteria were active cancer and insufficient information in patient journals.

2.3 Data retrieval and handling

The Neurosurgical department at Aalborg University hospital provided a list of patients who underwent SCS related operations in the aforementioned period. The list was reviewed to include

all the patients who had received a new SCS device and patients who underwent an IPG change in a previously implanted SCS device. Patients who exclusively underwent revision surgery were not included in this study.
The data was managed and kept in the data registration tool REDcap hosted at Aalborg University Hospital ensuring that all relevant data was safely logged for each specific patient.
Data was extracted through retrospective journal search where journals were read thoroughly by one observer. Data registration began on the day the patient underwent operation for IPG insertion.

The procedure codes KABD30 and KTAW99 were used to search specifically for operation procedures in journals, where data such as IPG implantation date was logged.
It was noted if the patient received a new SCS device or had an IPG change from a previously implant device.
Implant Trace Module in Clinical Suite was used to check if the patient received a TYRX envelope when it was not clearly stated in the patient journal.

Infections were registered if it was stated in the patient journal that the patient had received antibiotic medication beyond the standard antibiotic medication prescribed to each patient per- and postoperative, and the date of administration was set as the infection date. Furthermore, infections were subcategorized as pocket, systemic and/or wire infections.

It was registered if the patient underwent revision surgery or had the device removed, during the follow up period.
Individual details for each patient such as age, BMI and risk factors were also logged during journal analysis.
Data registration ended when the follow-up period was exceeded.

2.3.1 Definitions

This study defined infections as administration of antibiotic medication, oral and/or intravenous, suggesting a complication to the IPG implantation. This allowed the study to include patients with both minor and major infections.
Revision surgery was defined as an operational procedure where the patient did not receive a new IPG.
Risk factors were defined as patients who were active cigarette smokers, patients who had either type I or type II diabetes and/or patients who received immunosuppressive medications. Immunosuppressive medications were defined as steroids, methotrexate and antibody-based medication.

2.3.2 Follow up period

The follow up period was set at 100 days after the IPG implantation.

2.4 Statistical analysis

IBM SPSS statistical version 27 (IBM Co., Armonk, NY, USA) was used to analyze all the exported data from the REDcap datasheet. Continuous variables are presented as means and standard deviations. Categorical variables are presented as a percentage.

A Shapiro-Wilk test was used to test for normal distribution in continuous variables and if the data proved to be normally distributed a T-test was used to compare the TYRX and non-TYRX groups for similarity. When continuous data was not normally distributed a Mann–Whitney U test was used to test for similarity between the TYRX and non-TYRX groups.

A chi-squared linear by linear was used to test for association between groups in categorical nominal variables. Fisher's exact test was used when the groups to be compared were too small (n<5).
Statistically significant is defined as a p-value below 0.05.

2.4.1 Power

To estimate a relevant sample size, the following power calculations formula (32) can be used:

$$\mathbf{N = (C_{2\alpha} + C_{\beta})^2 \times S^2/\Delta^2}$$

$C_{2\alpha}$ describes the 2α fractile in the normal distribution, which is 1.96 at the alpha level of 0.05.
C_{β} is the β fractile in the normal distribution, set at 80% in this study, equaling 0.84.
S equals $(2*\sqrt{p}*(1-p))^2$, $p=(p_1+p_2)/2$, where p_1 is the infection rate in the non-TYRX group and p_2 is the infection rate in the TYRX group. Δ is the minimal difference in each group.
When calculated the estimated number of patients equals N.

3. Results

3.1 Study population

The study population included 198 patients, 50.5% of whom were women. The mean (±SD) age was 50.46±13.97 and the average BMI (n=177) was 28.22 ±5.37.
A Shapiro-Wilk test showed that age was normally distributed among the study population (p=0.728), however, this was not the case for BMI (p=0.007) where the median was 27.8.
Three different risk factors were chosen to be investigated in this study. In the population 28.57% were smoking (n=161), 7.58% had diabetes and 5.1% of patients were on immunosuppressive medication (n=195).
157 (79.3%) underwent an SCS procedure for the first time and 41 (20.7%) had a battery change operation.

18 (9.09%) of patients received a different treatment than the previously described standard treatment. All of these treatments were performed before insertion of IPG, and included alternative antibiotic treatment due to allergies, longer testing periods of implanted electrodes and no test period at all where an IPG device was implanted under the same initial procedure of electrode insertion. All deviations from standard treatment were performed before insertion of IPGs and were therefore not taken into account during statistical analysis.

3.1.1 Referral

Figure 1 shows the distribution of referral reasons for SCS operations. The largest group of patients was composed of different referral reasons categorized as others, which included disorders like chronic pain and other not well-defined conditions.

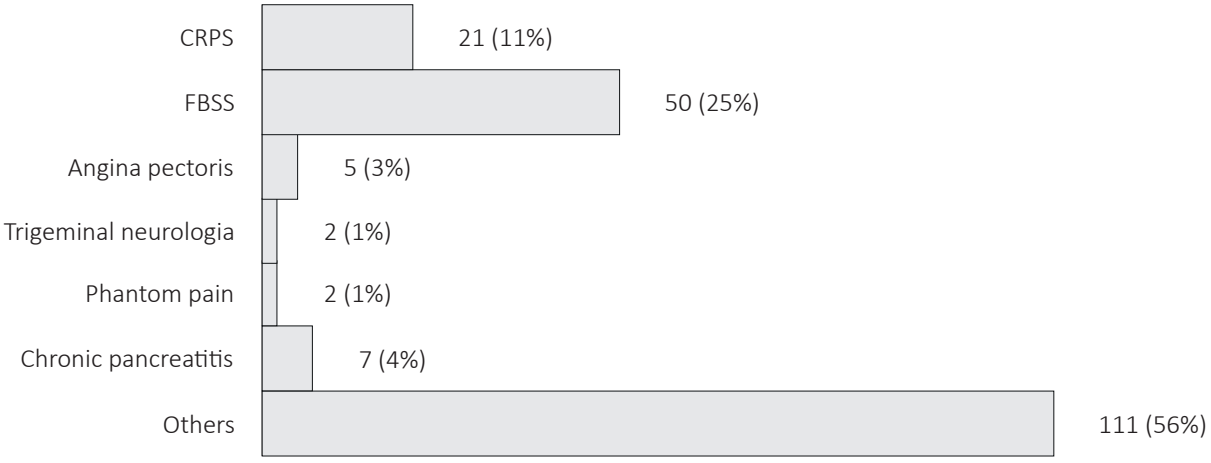

Figure 1: *Reasons for SCS procedure referral and their distribution - PLEASE NOTE; the referral reason "other" includes disorders like chronic pain and other not well-defined conditions. CRPS = Complex Regional Pain Syndrome. FBSS = Failed Back Surgery Syndrome.*

3.1.2 Comparison of groups

In table 2, the distribution of new SCS implants and battery change is presented. A chi-squared linear by linear revealed no association in new SCS implants and battery changes between recipients of the TYRX envelope and the patients who did not receive a TYRX envelope.

Table 2 - New SCS implant vs battery change in TYRX and non-TYRX recipients

	TYRX	non-TYRX	Total
New SCS implant (n=157)	77 (77%)	80 (81.63%)	157
Battery change (n=41)	23 (23%)	18 (18.37%)	41
Total	100	98	198

p=0.422

Age was tested for normal distribution in the TYRX and non-TYRX groups, both with a p-value (p=>0.05).
An unpaired t-test revealed no significant difference between age in TYRX and non-TYRX patients.
A Mann-Whitney-U test revealed no significant difference between BMI in the TYRX and non-TYRX groups.
A chi-squared test linear by linear showed no significant association between gender, smoking and diabetes when comparing the TYRX group and non-TYRX group. A Fisher's exact test revealed no association in immunosuppression medication between groups.
Table 3 shows the different data from the two groups including p-values from the above-mentioned statistical analysis.

Table 3 - Comparison of TYRX and non-TYRX groups

	TYRX	non-TYRX	*p*
Age (n=198)	50.2 ± 14.5	50.7 ± 13.45	0.8
BMI (n=177)	28.3 ± 5.55	18 (18.37%)	0.925
Gender (n=198)	46 women (46%) 54 men (54%)	54 women (55.10%) 44 men (44.90%)	0.201
Smokers (n=151)	20/76 (26.32%)	26/85 (30.59%)	0.135
Patients with DM (n=198)	9/100 (9%)	6/98 (6.12%)	0.44
Patients treated with Immunosuppressive medicine (n=195)	7/98 (7.1%)	3/97 (3.1%)	0.331

PLEASE NOTE; there were no statically significant findings.
DM = diabetes mellitus.

3.2 Infection

Within the 100 days of follow up after the IPG insertion operation 11 patients experienced an infection. Of the 11 infections, 9 were categorized as pocket infections, one as both pocket and systemic infection and one as a wire infection.
The total infection rate was 5.56% in this study.
The mean registered onset of infections was 25.64 ± 23.70 days.

3.2.1 Infection rate comparison between groups

Four patients in the TYRX group had an infection, and seven patients had an infection in the non-TYRX group, resulting in infection rates of 4% and 7.14%, respectively.
As shown in table 4, a two-sided fisher's exact test revealed no statistically significant association in infection between the TYRX and non-TYRX groups.

Table 4 - Incidents of infections in the TYRX and non-TYRX groups

	No infections	Infections	Total
Non-TYRX	91	7	98
TYRX	96	4	100
Total	187	11	198

p=0.262

3.2.2 Characteristics of infections between groups & risk association

Table 5 presents the different group characteristics of infections.
In the TYRX group the registered mean onset of infections was 28.25 ± 10.53 days after the operation and 24.14 ± 29.56 days in the non-TYRX group.
In the TYRX group all patients were treated exclusively with oral antibiotic medication. Intravenous antibiotic administration was only used in the non-TYRX group.
C-reactive protein (CRP), leukocytes, pathogen cultivation, revision surgery and SCS removal were only registered in the non-TYRX group.

Table 5 - Characteristics of infections

	All (n=198)	TYRX (n=100)	Non-TYRX (n=98)
Infection (n=198)	11 (5.56%)	4 (4%)	7 (7.14%)
Infection onset in days after battery insertion (n=11)	25.64 ± 23.70	28.25 ± 10.53	24.14 ± 29.56
Type (n=11)	9 pocket 1 pocket + systemic 1 wire	4 pocket	5 pocket 2 other
CRP (n=6)	83.3 ± 87.87	0	83.3 ± 87.87
Leukocytes (n=6)	10.73 ± 2.19	0	10.73 ± 2.19
Pathogen (n=4)	3 SA 1 SA + GGS	0	3 SA 1 SA + GGS
Antibiotic treatment (n=11)	5 PO 1 IV 5 Both	4 PO	1 PO 1 IV 5 Both
Revision (n=4)	4	0	4
Battery removal (n=3)	3	0	3

PLEASE NOTE; the similarity between the "All" and the "Non-TYRX" columns.
PO = Peroral. IV = intravenous. GGS = Group G Streptococcus. SA = Staphylococcus Aureus. CRP = C-reactive protein.

3.2.2.1 Risk association

This study included 41 patients who were active cigarette smokers, out of the 161 patients, where information regarding smoking was obtainable in the patient journals.
No statistically significant association between infections and smoking was found, results are shown in table 6.

Table 6 - Incidents of infections in non-smokers and smokers

	No infections	Infections	Total
Non-smokers	106	9	115
Smokers	44	2	46
Total	150	11	161

p=0.73

15 patients in this study had a comorbidity of diabetes.
A statistically significant association between having diabetes and developing an infection were found as is shown in table 7.

Table 7 - Incidents of infections in in patients with diabetes melitus

	No infections	Infections	Total
Patients without DM	175	8	183
Patients with DM	12	3	15
Total	187	11	198

*p=0.040**
** indicates statistically significant. DM = diabetes melitus.*

10 patients in this study received immunosuppressive medication.
No statistically significant association between immunosuppressed individuals and infection were found, as displayed in table 8.

Table 8 - Incidents of infections in patients receiving immunosuppressants

	No infections	Infections	Total
Not treated with Immunosuppressive medicine	176	9	185
Treated with Immunosuppressive medicine	9	1	10
Total	185	10	195

p=0.417

Of the 41 patients who were active cigarette smokers and the 15 who had a comorbidity of diabetes, 5 had both risk factors. A two-sided Fisher's exact test revealed no statistically significant association between infection when comparing the two risk factors simultaneously, as can be seen in table 9.

Table 9 - Incidents of infection between patient with two risk factors (diabetes + smoking)

	No infections	Infections	Total
Smoker	39	2	41
Patients with DM	12	3	15
Smoking + DM	5	0	5
Total	56	5	61

p=0.69
DM= diabetes mellitus.

3.3 Power calculation

Based on the results from this study, a new sample size can be calculated. With an Alpha level set at 0.05 and a power at 80% and with the infection rates from this study being 4% and 7.14% for the TYRX group and the non-TYRX group, respectively. Thus, a sample size of 1712 can be calculated, thereby estimating a distribution of 856 patients in each group.

4. Discussion

The findings of this study suggest an alignment with the studies exploring the effects of TYRX envelope in CIED implantations where multiple studies have shown the TYRX envelope infection rate reducing abilities (25,26,28,29).

This study found that the TYRX envelope has a non-statistically significant tendency to reduce infection rates in patients undergoing SCS procedures. Furthermore, recipients of the TYRX envelope who experienced an infection were treatable exclusively with oral antibiotics and did not receive revision surgery or have their devices explanted. This suggests that they had a milder infection than the non-TYRX recipients, who in some cases had their infections treated both with intravenous and oral antibiotics, revision surgery and in three instances removal of their devices.

Revision surgeries were not included in this study, as opposed to the Tarakji et al 2019, COMMAND and Hoelzer et al study. This was done to enable a follow up period of 100 days, without having to reset at revision surgeries, in order to include as many patients as possible.
However, an argument can be made that revision surgery should be included in the investigation, since Hoelzer et al found a tendency of a greater risk of infections in revisatory surgeries, and therefore would give a more accurate estimate of infection related to SCS operations (17).
This study did include IPG changes. Since it is a standardized procedure, it was chosen not to be categorized under revision surgery.

This study exclusively focused on infection as a complication in order to limit the extent of this study. This was accepted by the authors since the TYRX envelope has been associated with a high implantation success in CIED patients (25).
Suggestions could be made to further investigate other SCS procedure related properties of the TYRX envelope such as implantations success, allergic reactions, potentially toxic levels of antibiotic administrations, IPG related complications e.g., migration of the IPG or skin atrophy above the IPG.
This was however not investigated in this study but could potentially be included in future investigations.

It was noted that the testing period, before implantation of the IPG, varied among the patients. Hoelzer et al found that a testing period longer than 5 days is associated with greater infection risk (17). This was not investigated further in this study.
For future investigations length of the testing period should be considered a potential risk factor and therefore logged in the datasheets.

The infection rates in the group treated with the TYRX envelope were 4%, and 7.14% in the non-TYRX treated group. In the WRAP-IT study the TYRX recipients had an infection rate of 0.7% compared with 1.2% for non-TYRX CIED recipients.
The absolute percentages of the infection rates in this study are higher than in the WRAP-IT study, but the variation in percentage between TYRX and non-TYRX groups for both studies is approximately 40% (29).
The reason for the difference in absolute infection rates could be a result of different infection criteria. This study defined infection as antibiotic treatment after concluded post-operative antibiotic treatment, in order to include all infections.

This is different from the WRAP-IT study, which investigated major infections, defined as removal and/or revision of device and/or long-term antibiotic treatment in relation to infection suspicion (29). If this study only investigated major infections where patients who solemnly received PO antibiotic treatment would be excluded, this would result in an overall infection rate of 3.03% and infection rate in the TYRX group being 0% and 6.12% in the non-TYRX group.

The infection criteria of this study may also differ from the criteria in other studies investigating SCS infections in general. It was also noted that the absolute infection rates in this study were higher than in former studies investigating SCS related infection.

Holzer et al 2017 found the infection rate for SCS related procedures to be 2.45% (17). However, infection rates from other studies investigating infections in SCS procedures found higher infection rates such as 2.9 % and 4.5 % (33,34).

In the above mentioned three studies it is not clearly stated what the infection criteria were. In the study by Hoelzer et al it appeared to be based on clinical observations of wound characteristics and therefore differed from this study's infection criteria (17).
Since the infection criteria are not clearly stated in the other studies investigating SCS infection, it is difficult to suggest the exact cause of the infection rates being higher in this study.
Arguments could be made that an infection criteria based on antibiotic administration will include more infections since it is often administered as a prophylaxis at the least suspicion of infection, without there being actual pathogens present. For instance, when hyperemia is observed around the incision wound of the IPG or electrodes, as a simple inflammatory response due to the surgery.
This could result in a higher incidence of infection, given that these suspicions of infection do not always mean that there is an actual infection, regardless that they are treated as such.
Infection criteria should be clearly stated when investigating SCS procedures in future studies.

This study had a follow up period set at 100 days after IPG insertion. The follow up period was chosen to include as many patients as possible, as well as taking into consideration the deadline by which the study had to be concluded. This was accepted since the command study had had a short follow up period at 1.9-/+ 2.4 months and the Bendel et al study had a median infection onset after implantation of 27 days within a minimum follow up period of a year (14,25).
However, it could be argued that a longer follow up period is more optimal since infections related to SCS procedures have been observed outside a 100 day follow up period, which is also the case in CIED infections (14,29).
As arguments can be made for both a “short” and “long” term follow up periods, it is not considered a limitation of this study, as the follow up period of this study is more than three times the median time of infection onset in SCS surgery found in the Bendel et al study (14).

This study investigated the risk factors smoking, immunosuppressive treatment and diabetes, and their association to infection. There were no significant differences in the distribution of risk factors in the TYRX and the non-TYRX groups. Risk factors and infections were analyzed for the entire population, and not between the two groups. This was due to the fact that there were insufficient incidents of infections for each of the risk factors when dividing them into TYRX recipients and non-TYRX recipients.
However, the study did find an association between diabetes and infection. An association was not found between smoking and immunosuppressive treatment and infection.

4.1 Limitations

This study has a few limitations which should be taken into consideration regarding the results. Since this was a retrospective study, it was prone to selection bias e.g., non-randomized inclusion of subjects. The study was also liable to observatory bias e.g., recollection of subject details.
Data were not always available regarding BMI and smoking, and the data were in some instances therefore not collected for all individual patients.
Furthermore, it was not possible to investigate if a general practitioner had prescribed antibiotics to a patient, as it is not necessarily noted in the hospital journals of the patients, thereby potentially affecting the infection count. This could be argued very unlikely; hence all patients are encouraged to contact the neurosurgical department in case of complications.
As the power calculation suggests, the sample size in this study is too small, which is a considerable limitation. However, this was predicted as a result of the data currently available, based on the limited procedures performed at Aalborg neurosurgical department per year. The TYRX envelope was first introduced at Aalborg neurosurgical department in the spring of 2020 and considering the limited number of SCS procedures per year, a small population size had to be accepted, given the premises as a single center study.

5. Conclusion

The overall infection rate in this study was 5.56%, furthermore the infection rate was 4% in the TYRX group and 7.14% in the non-TYRX group.
The TYRX antibacterial envelope displayed a tendency to reduce infection rates, although this was not statistically significant. This, however, is likely due to the sample size, which should be much larger to enable statistically significant findings.
A difference between the TYRX group and the non-TYRX group could also be seen regarding the severity of the infections. Patients who had a TYRX envelope enclosed IPG, and an infection, were treatable solemnly with oral antibiotics.
Patients who did not receive the TYRX envelope were treated with a variation of oral and/or IV antibiotics, revision surgeries and in some cases device removal.
A key limitation of the study is the population size. Using the infection rates found in this study, a power calculating estimates a sample size of 856 patients in each group.
Further investigations of TYRX envelope in SCS procedures are needed and should consist of a multicenter prospective randomized control trial, to allow for a sufficient population size and thereby enable studies to conclusively determine if the TYRX envelope has similar infection reducing abilities in SCS procedures as in CIED procedures.

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