Comparing normal saline versus diluted heparin to lock non-valved totally implantable venous access devices in cancer patients: a randomised, non-inferiority, open trial

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Received 7 September 2012; revised 21 December 2012; accepted 11 February 2013

Background: Heparin has been used for years as a locking solution in totally implantable venous access devices. Normal saline (NS) might be a safe alternative for heparin. However, evidence of non-inferiority of NS versus heparin is lacking.

Patients and methods: We randomly allocated 802 cancer patients with a newly inserted port either to heparin lock (300 U/3 ml) or to NS lock groups in a 1:1 assignment ratio. The primary outcome was the number of functional

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complications, which was defined as ‘easy injection, impossible aspiration’ at port access. Secondary outcomes included all functional problems and catheter-related bacteraemia. We hypothesised that NS locks do not cause more functional problems and catheter-related bacteraemia than heparin locks. Non-inferiority is established if the upper limit of the confidence interval (CI) for the relative risk of NS versus heparin is <1.4.

**Results:** Three hundred and eighty-two patients from the NS group and 383 from the heparin lock group were included in the analysis. The incidence rate of our primary outcome (easy injection, impossible aspiration) was 3.70% (95% CI 2.91%–4.69%) and 3.92% (95% CI 3.09%–4.96%) of accesses in the NS and heparin groups, respectively. The relative risk was 0.94% (95% CI 0.67%–1.32%). Catheter-related bloodstream infection was 0.03 per 1000 catheter days in the NS group and 0.10 per 1000 catheter days in the heparin group.

**Conclusion:** NS is a safe and effective locking solution in implantable ports if combined with a strict protocol for device insertion and maintenance.

**Key words:** catheter lock, catheter-related infection, equipment failure, heparin, sodium chloride

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**introduction**

Totally implantable venous access devices (TIVADs) are widely used for intravenous therapy and blood sampling, mainly in cancer patients. Typically, diluted heparin is injected as a lock solution at the end of intravenous therapy to ensure device patency until the next drug administration. Several studies suggest that a 0.9% sodium chloride solution or normal saline (NS) is as effective as heparin in maintaining catheter patency in peripheral intravenous cannulas [1], arterial lines [2], apheresis [3], tunnelled, and non-tunnelled catheters [4]. For TIVADs, to the best of our knowledge, randomised studies comparing NS with the heparin lock are lacking.

An antimicrobial effect of heparin was claimed, but possibly could be attributed to added preservatives. Yet, preservative-free heparin at concentrations <6000 U/ml lacks antimicrobial properties [5]. Moreover, heparin could enhance catheter colonisation and biofilm growth [6]. Heparin administration also has potential risks, such as heparin-induced thrombocytopenia (HIT) [7], iatrogenic overdose, drug incompatibility, medication errors [8], and microbial contamination of multiple-dose vials [9]. In contrast, using a NS lock would simplify maintenance procedures and results in cost savings by reducing staff time, supplies, and drugs [1].

In the present study, we tested the hypothesis that, in TIVADs without specific valves or needleless connectors, a NS lock will not result in (i) more functional problems, and (ii) more catheter-related bacteraemia episodes compared with a heparin lock.

**methods**

**study design and patients**

This investigator-driven study is a single-centre, parallel-group, open-labelled, randomised non-inferiority trial. In a study with a heparin lock as standard of care, we found a 10% incidence rate of ‘impossible blood aspiration while injection is easy’ [10]. Based on these results, the non-inferiority margin was set at 4%, which corresponds with a relative risk of 1.4 for the group receiving NS. The study protocol was approved by the University Hospitals Leuven (UHL) Ethics Committee, and the trial was registered at ClinicalTrials.gov (NCT00994136).

Patients were recruited from UHL, Belgium, a teaching hospital where yearly a team of oncological surgeons insert 1350 TIVADs. Patient inclusion occurred from 23 January 2009 to 7 December 2010. Follow-up lasted until 5 June 2011. Eligible patients were older than 1 year, scheduled for a first TIVAD insertion through the superior vena cava (SVC) system, had an onco-haematological malignancy, and had a sufficient life expectancy to complete the planned follow-up of 180 days in the study centre. Exclusion criteria were adult patients who were unable to sign informed consent, inability to stand for a postoperative chest X-ray, patients with therapeutic intravenous heparin administration, history of HIT or abnormal clotting tests (international normalised ratio >2, or platelet count <40 000/mm³ or >1 000 000/mm³), or coincident participation in other clinical trials. Written informed consent was obtained preoperatively from adult patients or from parents in the case of children.

**randomisation and masking**

We randomly assigned patients in a 1:1 ratio following simple randomisation procedures (computerised random numbers) to two groups: NS group and heparin group. In the NS group, TIVADs were locked with NS. In the heparin group, a 3-ml heparin lock with a concentration of 100 U/ml heparin was used. The allocation sequence was concealed from researchers who enrolled patients according to sequentially numbered patient cards. These cards were stored in a separate room. Only after a patient signed the consent form the researcher collect the card assigning the patient to one of the two groups. The surgeon completed a case report form containing the type of access, chosen vein, and eventual perioperative problems.

**procedures**

Maintenance procedures were identical in both groups during TIVAD use. Devices were flushed with 10 ml of NS before and after blood sampling, at the end of intravenous therapy, every 8 weeks when the device was not in use, and with 20 ml of NS at the end of blood (components) transfusion or parenteral nutrition administration. In the heparin group, only before Huber needle removal, an additional heparin lock was injected after the NS flush. Before the start of the study, onco-haematology nurses were trained to perform correct techniques as pulsatile flush and positive pressure when injecting NS. Positive pressure was not exerted at Huber needle removal. Infection prevention measures included the use of 0.5% chlorhexidine solution with alcohol for skin disinfection before needle placement and for drenching the sterile gauze placed beneath the connection when the line is opened. A disconnected cap was never re-used. No sterile gloves were used.

The choice of TIVAD brand, namely Celsite® (B.Braun Medical, Boulogne Cedex, France) or Districath® (Districlass, Saint-Etienne, France), was left up to the surgeon’s discretion. Both devices have a titanium reservoir connected to an open-ended silicone catheter. Surgeons insert devices in an operating room using a venous cut-down technique and...

Patients were followed postoperatively for 180 days.

study end points

Our primary outcome measure was, at access, the ‘inability to aspirate blood while injection is easy’, also known as withdrawal occlusion and defined as ‘at the first attempt, impossible aspiration of 2.7 ml of blood while injection is easy’. We chose ‘easy injection, impossible aspiration’ as the primary end point, because this outcome has the highest incidence among all possible functional problems [12]. In the first month after the start of the study, one minor protocol change was made: we omitted ‘at first attempt’ from the malfunction definition. We observed that some nurses assessed the primary outcome i.e. the blood aspiration ability not only at the first attempt, but also after a 10-ml NS flush (the standard institutional procedure for blood sampling).

Secondary outcomes encompassed catheter-related bacteraemia and all other functional problems encountered at each port access. Catheter-related bacteraemia was chosen as a secondary outcome due to the relationship between heparin and biofilm growth [6]. We defined laboratory-confirmed bloodstream infection (BSI) as the presence of positive blood cultures from both the TIVAD and peripheral veins and fever or chills in the absence of other infection sources [13]. We screened retrospectively all microbial cultures available in the hospital information system. TIVAD functionality was assessed at every port access and recorded on a specially designed form.

formal quality control

Due to the relationship between functional problems and catheter tip position [14], an upright chest X-ray was taken postoperatively within 48 h to verify catheter tip position. We defined an optimal tip location as a point in the SVC situated 2 cm under the radiological projection of the inferior margin of the right main bronchus (RMB) on the chest X-ray [11]. All digital images were read by a senior chest radiologist (JV), unaware of the randomisation arm.

A second quality control was the assessment, at port access, of the presence of a correct lock solution according to the assigned group. This was done by withdrawal of the fluid present in the device; the fluid consisted of an admixture of blood and lock solution (heparin or NS). Nurses were taught to collect this fluid in a Vacutainer* tube without prior flushing of the device. However, some of them first injected NS (as mentioned previously) before performing the sampling meant for activated partial thromboplastin time determination. Therefore, this control step was skipped from June 2009. Alternatively, between December 2009 and June 2011, a bedside measure instrument, the Actalyke* MINI (Helena Laboratories, TX), was used by the study nurses in a convenience sample of 455 accesses to test the activated clotting time of the catheter contents. We validated bedside measurements by analysing the first 40 samples in the lab as well.

calculation of sample size

A withdrawal occlusion rate of 10% was expected in both groups. With the non-inferiority margin set at 4%, non-inferiority would be established if the upper limit of the confidence interval (CI) for the relative risk of NS versus heparin would be <1.4. Hence, based on a one-sided 95% CI for relative risk, 696 independent observations per group were needed to show, with 80% power, a non-inferiority for NS (NQuery Advisor, 5.0; Statistical Solutions Ltd., Cork, Ireland). Since multiple evaluations of each port were carried out for all patients (i.e. cluster sampling), the within-patient correlation was taken into account, because it might reduce the effective sample size. This loss of effectiveness was quantified by the design effect (DE) = 1 + ρ(m – 1), where ρ is the intraclass correlation (ICC) and m the average number of samples per patient. Assuming ρ = 0.3 and m = 5, the DE equals 2.2, such that 1532 evaluations are needed per group. If, on average, five samples can be taken per patient, this corresponds to 307 patients per group. To compensate for an expected dropout rate of approximately 30%, 400 patients per group needed to be recruited.

Two interim safety analyses were planned after inclusion of one- and two-thirds of the patients, wherein any evidence for inferiority of the NS lock would lead us to stop the study. To decide whether additional recruitment was needed, a blinded interim analysis was carried out shortly before the end of the planned recruitment phase. This analysis was carried out on 4327 accesses from 544 patients who completed the study at this point, and the needed sample size was recalculated, based on the observed overall withdrawal occlusion rate at this point in the study, the average number of accesses per patient, ICs, and the dropout rate. Based on this analysis, we deemed that additional recruitment of patients was unnecessary.

statistical analysis

A 95% two-sided CI was constructed to compare the relative risk of NS with that of heparin. We used a log binomial regression model [15] with generalised estimating equations (GEE) to take into account the evaluations of multiple port accesses per patient. Kaplan–Meier estimates were used to determine the number of port access evaluations and the number of catheter days to the occurrence of a first functional problem. Patients without a problem are censored at the last day of follow-up. Fisher’s exact test and a Poisson regression model with the natural logarithm of the number of catheter days as offset are used to compare the number of patients with BSI and the number of BSI episodes per 1000 catheter days, respectively. Analyses were based on intention-to-treat and carried out using the SAS software, version 9.2 (SAS Institute, Inc., Cary, NC).

results

patient and device characteristics

From the 2712 patients assessed for eligibility, 802 were included. After randomisation, 398 were assigned to receive a NS lock and 404, a heparin lock (Figure 1). The two groups were comparable in terms of patient and device characteristics (Table 1). Most of the patients suffered from breast cancer, and 3.5% of the patients were younger than 18 years. TIVADs were evaluated for 6126 accesses, covering 115 991 catheter days.

Mean distance between catheter tip location and target (RMB-based landmark plus 20 mm) was 3.1 mm (SD 23.5 mm) for all devices. Results of catheter content assessment tests were confirmed to the assigned catheter lock solution in 427 (93.8%) cases.

functional problems and catheter-related bacteraemia

At access, injection problems (difficult or impossible injection) were less frequently encountered than aspiration problems (difficult aspiration, incomplete filling of the Vacutainer* tube, or impossible aspiration). ‘Easy injection, impossible aspiration’ occurred in 109 (3.5%) of 3109 accesses and in 115 (3.8%) of 3017 accesses of patients assigned to the NS group and heparin group, respectively. Taking into account, the variation in the number of port accesses between patients, the risks (GEE model) were 3.70% and 3.92%, respectively, with a
relative risk of 0.94% (95% CI 0.67%–1.32%) in favour of NS (Table 2).

In total, 78 (20.4%) patients in the NS group and 73 (19.1%) in the heparin group experienced at least one episode of ‘easy injection, impossible aspiration’. Survival analyses showed that the number of accesses (Figure 2) and time elapsed until first occurrence of the primary outcome event (Figure 3) were comparable between the two groups.

Laboratory-confirmed BSI was present in two (0.03/1000 catheter days) and six patients (0.10/1000 catheter days) in the NS and heparin groups, respectively. The differential time to positivity (DTTP) was more than 2 h for three patients in whom a set of blood cultures was taken, both via the TIVAD and a peripheral vein. DTTP could not be determined in five patients for which a blood culture was only carried out through the TIVAD. Table 3 summarises details of germs and dwell time at the onset of positive blood cultures. In three cases, all assigned to the heparin group, the TIVAD was removed due to infection with Staphylococcus aureus (pocket infection), Candida glabatra, or Staphylococcus epidermidis.

We found retrospectively in the electronic hospital information system 56 ultrasound investigations on suspicion of central venous thrombosis (CVT). The diagnosis of CVT was confirmed in 24 patients: 13 (3.3%) in the heparin group and 11 (2.8%) in the NS group. In five patients with CVT, two in the heparin and three in the NS group, the device was removed directly after completion of the chemotherapy within 180 days of study follow-up. In the heparin group, other reasons for prematurely removal are the following: device malfunction together with a suboptimal tip location (n = 2) and additional sleeve formation (n = 1), catheter sleeve formation with shoulder pain and aberrant catheter course (n = 1), intracardial thrombus formation (n = 1), and elective removal (n = 3). In the NS group, another five ports were removed due to: infection suspicion (n = 2), skin erosion above port (n = 1), and elective removal (n = 2).
One of the patients in the heparin group developed HIT.

Other complications such as pneumothorax at insertion,

bleeding, arrhythmias, pinch-off problems with catheter fracture, migration, or embolisation were not reported.

**Discussion**

TIVAD manufacturers initiated the heparin lock procedure in the early 1980s. Today, a variety of locking procedures are found in guidelines: with or without heparin (10–100 U/ml) and ‘according to the manufacturer’s recommendations’ [16–19]. We conducted a literature search of Pubmed and CINAHL using a combination of the following: the MeSH terms ‘catheterisation, central venous’, and ‘heparin’, and the language limits English, French, German, and Dutch. We used as inclusion criteria studies that report functional outcomes on the use of heparin versus NS lock in TIVADs, without specific valves or needleless connectors. No studies were found. However, manual search revealed one retrospective report [20]. Therefore, we designed a first-of-its-kind randomised, controlled trial comparing NS and heparin for TIVAD locking.

A NS lock was non-inferior to heparin with regard to the problem of ‘easy injection, impossible aspiration’ in our series. Our incidence rate for ‘easy injection, impossible aspiration’ was lower (3.5%–3.8%) than reported rates, which vary between 5.9% and 26% of accesses [12]. The low rate in the present study could be explained by two facts. First, one team of oncological surgeons with an extensive experience in correct intraoperative catheter tip location inserts all implantable ports [11]. Indeed, only 3 of 796 TIVADs were removed prematurely due to malfunction problems associated with an incorrect tip position. Secondly, a dedicated venous access support team is available for troubleshooting of TIVADs, for developing hospital-wide procedures, and for educating all staff that deal with TIVADs [21]. Nurses are individually trained by the team to use a manual palpable flush technique [22], followed by a positive pressure locking technique, which could influence positively incidence numbers. These were initiated together with a reduction in the volume and frequency of heparin use, in 2008 when heparin became scarce. Indeed, our current incidence numbers are lower than those published before 2008 [10].

The incidence rate in the present study for laboratory-confirmed BSI of 0.03/1000 and 0.10/1000 catheter days in the NS and heparin groups, respectively, is lower than that in the published studies [23–25]. Furthermore, only three TIVADs (0.38%) were prematurely removed due to infection, much less than recently reported rates (3.5%–8.9%) [23, 25, 26]. This may be due to our strict sterile insertion procedure and again on the availability, skill, and training mission of the institution’s multidisciplinary venous access team. These two measures could effectively reduce catheter-related BSI incidence [27]. The 2011 Healthcare Infection Control Practices Advisory Committee-Centers for Disease Control (HICPAC-CDC) guidelines strongly recommend this policy based on solid scientific endorsement [28].

Our study has a number of strengths. We chose a non-inferiority design with a non-inferiority margin defined in terms of relative risk, not in terms of an absolute difference in risk. As such, the margin was not too liberal due to an observed event rate being lower than the expected one [29].
Table 2. Evaluation of functional outcomes at access

<table>
<thead>
<tr>
<th>Observed rates as the number of accesses, N (%)</th>
<th>NS</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy injection, impossible aspiration</td>
<td>109 (3.5)</td>
<td>115 (3.8)</td>
</tr>
<tr>
<td>Injection problems</td>
<td>12 (0.4)</td>
<td>25 (0.8)</td>
</tr>
<tr>
<td>Aspiration problems</td>
<td>168 (5.4)</td>
<td>174 (5.8)</td>
</tr>
<tr>
<td>Injection and/or aspiration problems</td>
<td>176 (5.7)</td>
<td>192 (6.4)</td>
</tr>
</tbody>
</table>

As risk from a model with GEE

<table>
<thead>
<tr>
<th>Event</th>
<th>% (95%CI)</th>
<th>% (95%CI)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy injection, impossible aspiration</td>
<td>3.70 (2.91–4.69)</td>
<td>3.92 (3.09–4.96)</td>
<td>0.94 (0.67–1.32)</td>
</tr>
<tr>
<td>Injection problems</td>
<td>0.40 (0.23–0.71)</td>
<td>0.81 (0.51–1.28)</td>
<td>0.50 (0.24–1.03)</td>
</tr>
<tr>
<td>Aspiration problems</td>
<td>5.57 (4.49–6.91)</td>
<td>5.86 (4.69–7.29)</td>
<td>0.92 (0.70–1.30)</td>
</tr>
<tr>
<td>Injection and/or aspiration problems</td>
<td>5.87 (4.75–7.24)</td>
<td>6.38 (5.15–7.88)</td>
<td>0.92 (0.68–1.24)</td>
</tr>
</tbody>
</table>

The number of evaluations per patient is not constant. Therefore, the estimated risk for a functional problem obtained with the logistic model with GEE does not correspond exactly to the observed percentage of access problems.

NS, normal saline; GEE, generalised estimating equations.

Figure 2. Kaplan–Meier curves for the number of accesses to first ‘easy injection, impossible aspiration’ event.

Figure 3. Kaplan–Meier curves for the time to first ‘easy injection, impossible aspiration’ event.
Similarly, the choice for reporting a two-sided 95% CI instead of a one-sided 95% CI fits within a conservative approach. A two-sided 95% CI for non-inferiority purposes is equivalent to a one-sided C.I with $\alpha = 2.5\%$. Further, since the required number of patients not only depended on the non-inferiority margin, but also on the event rate, the mean number of port access evaluations per patient and the within-patient correlation, a blinded interim analysis was carried out to safeguard the statistical power of the trial.

We could limit the dropout rate to 4.6%, and this is not statistically different between the two groups (5.5% and 3.8% for NS and heparin, respectively; $P = 0.26$). However, we noticed a higher probability of dropout for males and older patients.

Finally, based on the recommendations of a systematic review on functional complications in implantable ports, we opt for a precise and operational definition of malfunction [12]. Before study start, the description of the primary outcome as a ‘easy injection, impossible aspiration’ was thoroughly explained to the nurses who were used to more vague terms, e.g. catheter occlusion or blockage.

Our study has some methodological limitations. First, due to logistic reasons, it was not possible to blind lock solutions. Secondly, we failed to recruit >30% of all eligible patients mainly due to strict inclusion criteria. Thirdly, the study was conducted in a tertiary hospital with a dedicated team of surgeons and a venous access support team, factors that could have influenced the results positively. Finally, only 329 (43.0%) patients were followed for the entire planned 180 days. The mean number of catheter days for all patients was 151.6 days. Indeed, most of the chemotherapy regimens include six treatment sessions, every three or four weeks, which results in 105–140 days of active TIVAD use.

Our study provides further new insights in the field of locking implantable ports. In contrast to studies carried out in short-term catheters, our results show evidence that implantable ports remain patent, even if not used for weeks (e.g. between chemotherapy cycles). Moreover, we found no more malfunctions when using NS instead of heparin as catheter-locking solution, although nurses did not apply positive pressure at Huber needle removal. Yet, for years, the use of heparin has been justified by prevention of occlusion due to blood influx at the catheter tip generated at Huber needle removal, when the port septum is slightly lifted while removing the needle. Indeed, Lapalu et al. [30] found, in an in vitro experiment, an average of 3.49 µl (SD 1.65 µl) influx of blood when the Huber needle was withdrawn without the application of positive pressure. Our clinical results do not support the need for exerting a positive pressure on the plunger of the NS syringe during needle removal.

Our study is the first to claim non-inferiority of NS compared with heparin to lock TIVADs. Consequently, we propose that additional prospective studies be done, which (i) use the same primary outcome, (ii) allow broader inclusion criteria, and (iii) involve multiple centres.

We conclude that a heparin lock, before Huber needle removal, can safely be omitted, providing that a strict protocol for TIVAD insertion and maintenance is observed. The confirmed non-inferiority of NS versus heparin may support the decision to evolve from heparin lock use to heparin-free hospitals for catheter management.

acknowledgements

We thank Dr C. Leonard (Exact Science Communications, LLC) for copyediting a draft of the manuscript. The copyediting was funded by Leuvens Kankerinstituut, Leuven, Belgium. We thank Dr Borremans for her assistance, all patients for their participation in the study, and the nurses and doctors for their skilled contribution.

funding

The study was partially funded by Leuvens Kankerinstituut and by BBraun Belgium.

disclosure

GAG, MJe, and MS have received speaking honoraria from BBraun. MS has received educational research grants from BBraun and Opus medical. GAG has received travel grants from Opus medical, MJe from BBraun and Opus Medical, CJ from BBraun, Medri, and MS from BBraun and C. R. Bard. MS has been a consultant of BBraun. The remaining authors have declared no conflicts of interests.

table 3.

<table>
<thead>
<tr>
<th>Microbial species</th>
<th>NS</th>
<th>Heparin</th>
<th>Statistical test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>0 (0.5)</td>
<td>2 (27–29)</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>1 (67)</td>
<td>3 (56–77)</td>
<td>P = 0.18</td>
</tr>
<tr>
<td>Staphylococcus hominis</td>
<td>1 (35)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>0 (0)</td>
<td>1 (102)</td>
<td></td>
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</tbody>
</table>

*The number of cases with specific microbe. Numbers within the parentheses represent the number of catheter days between insertion and positive blood cultures for each of the positive cases.

NS, normal saline.

references


