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Peer Review File

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Reviewer A

Dear authors,

Thank you for the opportunity to Review your trial protocol. The plan is to randomise between US guided puncture of different vein locations and the primary outcome is patient satisfaction.

To further improve your protocol I have made several suggestions (marked as comments) in the attached PDF file.

In brief, the are some major concerns regarding randmisation procedures, definitions of late complications and the follow-up interviews and the statement at the end re sample size.

Response:

We are very grateful for your kind suggestions, and these suggestions are very helpful to further improve our protocol. There are 22 comments or suggestions you provided in the attached PDF file, and we response to your comments and suggestions point by point in the following part.

1. the title is informatiive and relevant

Response:

Thank you for your positive comment.

2. Abstract is good

Response:

Thanks for your positive comment.

3. FemaleS?

Response:

We are sorry for our spelling mistake and we have changed “female” to “females” in the manuscript (Introduction, line 63).

4. Please provide a rationale as why you don't use CONSORT (which is more common)

Response:

Thanks for your kind suggestion. CONSORT is common to report randomize clinical

trials while SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) is usually used to report clinical trial protocol. APM required authors to prepare the study protocol for interventional trials according to the SPIRIT guidelines (http://apm.amegroups.com/pages/view/guidelines-for-authors#content-2-7-1), so we used the SPIRIT checklist but not CONSORT.

5. I am having trouble understanding why these groups are excluded. How do you determine the presence of depression/anxiety, and finally do you usually exclude DVT patients from SCV/AxV insertion?

Response:

Thanks for your kind suggestion. As we known, it is not easy to evaluate patients with anxiety or depression unless we make a questionnaire of anxiety or depression for every patient. In our study protocol, we will take Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) for every patient. We have made some changes in the exclusion criteria part (Methods, Patient Selection, line 96-line 98).

Patients with one or more of these following situations will be excluded: (I) confirmed distant metastasis because they may pass away before port removal; (II) diagnosed with anxiety or depression with Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) questionnaire because anxiety or depression may have impact on patient comfort assessment; (III) have a history of deep venous thrombosis (DVT) or other coagulation disorders because we also compare complications including thrombosis between these two arms of patients in our study. As a matter of fact, we will not exclude DVT patients from CVC insertion in clinic practice, and we just exclude these patients from our study; (IV) are not able to understand the comfort scale questionnaire or cooperate with our work.

6. Further, all exclusion criteria will impair the external validity of the trial (less pragmatic appraoach)

Response:

Thanks for your advice. We strongly agree with you that all exclusion criteria will impair the external validity of the trial. However, there will be many confounding factors if we include all patients in our study. As a matter of fact, only a small percentage of patients meet these exclusion criteria. Meanwhile, we have explained why we exclude these patients in our study in the previous response.

7. The randomization procedure must be explained in more detail - Opaque envelopes? Computerbased? Online?

Response:

Thanks for your kind suggestion and we are sorry that we did not explained the randomization procedure detailly.

A randomization chart will be generated using Microsoft Excel. Randomization will be performed by one of the researchers who will not take neither operation, data collection nor analysis in this study. We will prepare opaque, sealed envelopes each containing a slip of paper with a computer-generated description of whether the patients will be assigned to IJV group or AxV/SCV group. We have described the randomization procedure in detail in our manuscript (Methods, Study Design, line 105-line 110).

8. This will introduce

Response:

Thanks for your suggestion. Dr. Bao and Dr. Deng are both doctors in the Department of Breast Tumor Center and participants in this study. We have introduced this in our manuscript (Methods, Study Design, line 113-line 114).

9. Where will the patients be screened? And by whom?

Response:

Thanks for your kind suggestion. Breast cancer patients who are about to receive chemotherapy in our hospital, Sun Yat-sen Memorial Hospital, Sun Yat-sen University will be screened and enrolled in our study by researchers who will not take neither operation, data collection nor analysis in this study. We have described this part in our manuscript (Methods, Study Design, line 114-line 116).

10. What about sedatives? Do you ever give that during IVAP implantation? This must be stated and/or reported

Response:

Thanks for your kind suggestion. We will not give sedatives to patients during IVAP implantation because patients can cooperate with us well with local anesthesia. We have stated this in our manuscript (Methods, Implantation Procedure, line 143).

11. Will the interview be conducted by the researchers or by letters? Will patients be in a bias-free surrounding when they answer??

Response:

Thanks for your kind suggestion. The interview of patient comfort assessment will be conducted by the researchers face by face on day 1 and conducted with telephones on day 2 and day 7. All patients will receive assessment of comfort with a comfort

scale table for three times independently. We have added this description in our manuscript (Methods, Outcome Measures, line 157-line 159).

12. Secondary outcomes?

Response:

Thanks for your kind suggestion. These outcome measures (I) duration of procedure (minutes); (II) early complications rate and (III) late complications rate are all secondary outcomes. We have change “other outcome measures” to “secondary outcome measures” in our manuscript (Methods, Outcome Measures, line 167).

13. All of these complications must be defined (or refer to paper where definitions are clear)

Response:

Thanks for your kind advice and we have defined all the complications in our manuscript. Early complications include wire advancement difficulties, inadvertent artery puncture, catheter misplacement, pneumothorax or subcutaneous hematoma. Late complications include port related infection, CVC related DVT, and catheter complications such as tip dislocation, catheter rupture or loss of patency.

All these complications are defined as following:

1) Wire advancement difficulties: failure puncture or wire advancement for three times or more.
2) Inadvertent artery puncture: pulsatile blood reflux through the needle observed during the procedure.
3) Catheter misplacement: catheter tip identified at any place other than the superior vena cava on the chest X-ray.
4) Pneumothorax: characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung on the chest X-ray.
5) Subcutaneous hematoma: characterized by a localized collection of blood, usually clotted, in space near the point of puncture.
6) Port related infection: isolation of the same organism from a blood culture and from a semiquantitative or quantitative culture of a catheter segment, accompanied by clinical symptoms of bloodstream infection without any other apparent source of infection.
7) CVC related DVT: vein thrombosis is defined as thrombosis on the tube wall established by color Doppler ultrasound examination.
8) Tip dislocation, catheter rupture: tip dislocation or catheter rupture on the chest X-ray.

9) Loss of patency: the infusion port or tube is obstructed and drug cannot pass through the catheter.

We have stated this in our manuscript (Methods, Outcome Measures, line 177-line197).

14. If the randomization process is valid, you should not analysis baseline differences between the groups.

Response:

Thanks for your kind suggestion. We agree with you and we will only report the baseline information of these two groups but not compare them. We have made the modification in the manuscript (Discussion, line 254-line 255).

15. Not cancer patients and not implanted ports.

Response:

Thanks for your kind suggestion. Yes, there were no cancer patients or implanted ports in this study from NEJM, which was quite different from our study. Our research will only include breast cancer patients with infusion ports for study. We have stated this in our manuscript (Discussion, line294-line 295).

16. There is a potential risk that the AxV/SCV groups will develop more DVTs than those with IJV catheters because of the smaller vein diameter more distally. What are your thoughts on this?

Response:

Thanks for your advice and comment.

There are many risk factors of catheter related thrombosis, such as age, duration of implantation, whether use of anti-coagulation drugs and so on. Whether risk of catheter related thrombosis varies according to the site of insertion remains controversial. In one trial, catheter-related thrombosis occurred in 21.5 percent of the patients with femoral venous catheters and in 1.9 percent of those with subclavian venous catheters (1). In an observational study, the risk of thrombosis associated with internal jugular insertion was approximately four times the risk associated with subclavian insertion, which means subclavian venous catheterization carries the lowest risk of catheter-related thrombosis (2). Some other researches also indicated that CVC-related venous thrombosis in subclavian vein catheterization is significantly lower than that in internal jugular vein catheterization (3-5).

However, another study indicated that CVC-related venous thrombosis in subclavian vein catheterization is higher than that in internal jugular vein (6).

In our opinion, whether risk of catheter related thrombosis varies according to the site

of insertion is still controversial and needs more evidence. Our prospective clinical trial will provide more evidence in the future.

1.Merrer J, De Jonghe B, Golliot F et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial.[J] ., 2001, 286: 700-7.

2. Timsit J F, Farkas J C, Boyer J M et al. Central vein catheter-related thrombosis in intensive care patients: incidence, risks factors, and relationship with catheter-related sepsis.[J] ., 1998, 114: 207-13.

3. Hrdy Ondrej, Strazevska Eva, Suk Petr et al. Central venous catheter-related thrombosis in intensive care patients - incidence and risk factors: A prospective observational study.[J] ., 2017, 161: 369-373.

4. Liu Gao, Fu Zhi-Qing, Zhu Ping et al. Central venous catheter-related thrombosis in senile male patients: New risk factors and predictors.[J] ., 2015, 35: 445-449.

5. Shah A, Smith A, Panchatsharam S, Ultrasound-guided subclavian venous catheterisation - is this the way forward? A narrative review.[J] ., 2013, 67: 726-32.

6. Ducatman B S, McMichan J C, Edwards W D, Catheter-induced lesions of the right side of the heart. A one-year prospective study of 141 autopsies.[J] ., 1985, 253: 791-5.

17. Is that feasible?

Response:

Thanks for your advice. In our study protocol, researchers who take interview for patient comfort will not perform port implantation for patients, which is “single-blind”. However, it is not feasible to reach “double blind” in our study because it is impossible to be blind to patients.

18. The results will have a limited external validity

Response:

Thanks for your kind suggestion and we agree with you that the results will have a limited external validity. Just as we discussed, we will perform a prospective multicenter survey with larger sample size to compare comfort between IJV puncture and AxV/SCV puncture may be necessary in the future.

19. Please explain why the sample size is too small - you previously stated that your sample is sufficient. There is an ethical dilemma if you chose to include 200 patients and this sample is too small to answer your research question.

Response:

Thanks for your kind suggestion. As we mentioned in the part of Method, Sample size: we made a preliminary study with a small amount of cases (30 cases), which indicated that patient comfort scale (mean ± standard deviation) was 1.00±0.707 in IJV group and 0.63±1.061 in AxV /SCV group in D7 after CVC puncture. The required sample size was calculated using an estimation formula based on the different means between two groups. Setting the two-sided significance level (α) at 0.05 and statistical power(1-β) at 0.8, a minimum sample size of 90 participants per group (180 participants in total) was estimated to provide sufficient statistical power for detecting the difference between two groups. Considering a 10% loss to follow-up, we plan to enroll 100 patients in each arm, for a total of 200 patients. We think sample size of 200 patients is with sufficient efficiency to answer this question (Methods, Sample size, line 123-line 134).

20. What about complications - if there are differences in complications rates (pnthx or DVT) these will surely affect patient satisfaction? You will problably not catch these perceptions since they are late complications and your interview follow-up ends after 7 days. I suggest interviewing after 90 days or at removal, whichever comes first.

Response:

Thanks for your kind suggestion. We agree with you that complications (pnthx or DVT) will affect patient satisfaction. Well, in our study, we choose to compare patient comfort of catheter position instead of patient satisfaction, and we think these complications will not affect patient comfort. At the same time, we found patient comfort may be with no obvious difference between these two arms after several weeks of port implantation in our preliminary work. Therefore, we do not interview patient comfort at a long time point.

21. You need a box where you report those screened, but not randomized

Response:

Thanks for your kind advice. We have changed the flow diagram of the progress in our manuscript (Figure 1, line 453-line 454).

22. Lost to follow-up?

Response:

Thanks for your kind advice. We have changed the flow diagram of the progress in our manuscript (Figure 1, line 453-line 454).

As a matter of fact, almost all the patients will receive port implantation and

chemotherapy (if it is necessary according to the NCCN guideline) after being diagnosed breast cancer in our hospital. Only very few patients will be lost to follow up in our hospital.

Reviewer B

The publication of the description of a research project not yet started is a very unusual and sometimes accepted procedure for meta-analyzes of great interest such as the Cochrane Library sometimes does. In the case of this certainly interesting study, I would like to see endings and not the "intention to perform a trial".

I would advise authors to review some features of their study design.

Response:

We are very grateful for your kind suggestions, and these suggestions are very helpful to further improve our protocol. Here we introduce our protocol as part of our study project since a protocol after peer-reviewed can greatly improve the study. Thanks for your interest in our study and we have begun to enroll patients in this study. We will report the results of this study when the study ends.

The comfort scale presented by the authors has not been validated in any specific paper. It is very reductive and has as its great limitation that it is probably applicable only to the Chinese population. This could be a major limitation in view of a future publication of the results. I suggest to use the chinesization QASICC Marcy's scale of QoL evaluation (Ye Liu, Lei Xu, Min Jiang, et al The Journal of Vascular Access Article first published online: May 6, 2020 https://doi.org/10.1177 / 1129729820920528) that is the only accepted scale for TIVADs QoL and patient's satisfaction evaluation.

Response:

We are sorry that we did not introduce and discuss the comfort scale in detail in our manuscript. As a matter of fact, the comfort scale presented in our manuscript was a Visual Analogic Scale, which was modified from other papers which were validated (1-5).

In reference 1, authors assess patient comfort by Visual Numerical Scale ranging between 1 (extreme discomfort) and 5 (very comfortable).

In reference 2, the authors used a satisfaction score (0-5) to access local discomfort, and high score indicates high local discomfort.

In reference 3, patient discomfort was assessed using an unmarked 100 mm visual analogic scale from “no discomfort” to “maximal imaginable discomfort”

In reference 4 and 5, authors used a visual analogue scale to assess patient comfort

at 0 cm with “very uncomfortable” and 10 cm with “very comfortable”.

At the same time, we also read the article you suggested to us (Liu Ye, Xu Lei, Jiang Min et al. Chinesization of the quality of life assessment, venous device-port, and its reliability and validity tests for patients with breast cancer.[J] .J Vasc Access, 2020, undefined: 1129729820920528). This article is very helpful to us. The authors introduced an effective assessment tool to access the quality of life with good reliability and validity in breast cancer patients with different implantation sites for totally implanted venous access devices in northern China. However, the primary outcome measure is the patient comfort, which is slightly different from quality of life. The component of quality of life contains the following aspects (1) aesthetics and privacy, (2) impact on professional activities, social, and sports and impact on daily activities, and (3) pain, contribution to comfort of the treatment, local discomfort, and overall satisfaction, and our study just focuses on patient comfort. This assessment tool may be useful for us to take overall assessment of quality of life for patients in future research. We have discussed this in the discussion (Discussion, line 258-line 272).

1. Mauri Tommaso, Galazzi Alessandro, Binda Filippo et al. Impact of flow and temperature on patient comfort during respiratory support by high-flow nasal cannula. [J] .Crit Care, 2018, 22: 120.

2. Babu K Govind, Suresh Babu M C, Lokanatha D et al. Outcomes, cost comparison, and patient satisfaction during long-term central venous access in cancer patients: Experience from a Tertiary Care Cancer Institute in South India.[J] ., 2016, 37: 232-238.

3. Frat Jean-Pierre, Thille Arnaud W, Mercat Alain et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure.[J] .N. Engl. J. Med., 2015, 372: 2185-96.

4. Russo Riccardo, Wallace Denise, Fitzgerald Paul B et al. Perception of comfort during active and sham transcranial direct current stimulation: a double blind study.[J] .Brain Stimul, 2013, 6: 946-51.

5. Wallace Denise, Cooper Nicholas R, Paulmann Silke et al. Perceived Comfort and Blinding Efficacy in Randomised Sham-Controlled Transcranial Direct Current Stimulation (tDCS) Trials at 2 mA in Young and Older Healthy Adults.[J]. PLoS ONE, 2016, 11: e0149703.

I suggest a better and concise clear definition and list of the adverse events and their assessment.

Response:

Thanks for your kind suggestions and we are sorry that we did not show clear definition of adverse events and their assessment in our manuscript. Early complications include wire advancement difficulties, inadvertent artery puncture, catheter misplacement, pneumothorax or subcutaneous hematoma. Late complications include port related infection, CVC related DVT, and catheter complications such as tip dislocation, catheter rupture or loss of patency.

Here we add concise clear definition and list of the adverse events and their assessment in our manuscript (Methods, Outcome Measures, line 177-line197).

Wire advancement difficulties: failure puncture or wire advancement for three times or more.

Inadvertent artery puncture: pulsatile blood reflux through the needle observed during the procedure.

Catheter misplacement: catheter tip identified at any place other than the superior vena cava on the chest X-ray.

Pneumothorax: characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung on the chest X-ray.

Subcutaneous hematoma: characterized by a localized collection of blood, usually clotted, in space near the point of puncture.

Port related infection: isolation of the same organism from a blood culture and from a semiquantitative or quantitative culture of a catheter segment, accompanied by clinical symptoms of bloodstream infection without any other apparent source of infection.

CVC related DVT: vein thrombosis is defined as thrombosis on the tube wall established by color Doppler ultrasound examination.

Tip dislocation, catheter rupture: tip dislocation or catheter rupture on the chest X-ray.

Loss of patency: the infusion port or tube is obstructed and drug cannot pass through the catheter.

Anxiety and depression as exclusion criteria is very vague. How do the authors intend to evaluate them?

Response:

Thanks for your kind suggestion. As we known, it is not easy to evaluate patients with anxiety or depression unless we make a questionnaire of anxiety or depression for every patient. In our study protocol, we will take Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) for every patient. We have made some changes in the exclusion criteria part (Methods, Patient Selection, line 96-line 98).