Supplemental material (SM):

Central or peripheral catheters for initial venous access of ICU patients: a randomized controlled trial

SM 1

A) Inclusion criteria

Drugs and doses pre-defined in protocol
- Thiopental, regardless of dose, for an expected period shorter 24 hours,
- Epinephrine at a dose less than or equal to 2 mg / hour,
- Norepinephrine at a dose less than or equal to 2 mg / hour,
- Dopamine or Dobutamine at a dose not exceeding 10 mg / kg / min,
- Amiodarone: less than 3 ampoules per day, for an expected period shorter than 3 days
- Vancomycin: discontinuous infusion of a dose < 1 g / day
- Amphotericin B, for an expected period < 3 days.

Venous access: insertion and maintenance difficulties
Two failed-attempts to insert a PVC
Need to replace a PVC twice a day, two days in a row
Need to replace a PVC once a day, three days in a row

B) Non-inclusion criteria
- Age under 18,
- pregnant or breastfeeding women
- refusal to participate in the study
- contra-indication to PVC (extreme cutaneous damage [extensive burn, Lyell syndrome])
- need for a drug listed above outside the boundaries of doses
- contra-indication to CVC (such as severe haemostatic disorders, high suspicion of endocarditis, predictable insertion difficulties according to the attending physician).
C) Crossover criteria

1) Increase in drug dosage exceeding the upper limit of the inclusion criteria:
For example: increase in norepinephrine above 2 mg/hour

2) Impossibility or great difficulties in inserting or maintaining a PVC:
- if a patient is randomized to the PVC and insertion of this catheter is not possible, than the patient is automatically crossed-over to the CVC group.
- in patients randomised to the PVC group, if after initial PVC insertion, the need to replace a peripheral catheter more than twice a day, two days in a row, due to the poor quality of the venous capital, then the patient is crossed-over to the CVC group.
SM 2 : List of complications

A) Major complication

1. Mechanical complications

1.1 During CVC insertion
- Necessity to change site insertion
- Insertion success after two changes of site insertion (two failed attempts)
- Failure to insert CVC after at least trials at two different sites
- Arterial puncture
- Vessel injury (requiring surgical repair)
- Pneumothorax
- Hemothorax
- Local haematoma of at least 3 cm²
- Mediastinal haematoma
- Gas embolism
- Embolism of the wire

1.2 During PVC insertion
- Impossibility to place a PVC
- More than 5 attempts to insert PVC

1.3 During CVC maintenance
- Gas embolism

1.4 During PVC maintenance
- Maintenance of catheter or catheter insertion impossible
- Subcutaneous diffusion ≥ 5x5cm or necrosis or blister ≥ 3x3cm

2. Infectious complications

2.1 CVC complications
- Localised erythema (>2cm from insertion site)
- Unexplained bacteraemia: positive blood culture in the absence of obvious infectious focus.
- Catheter-related bacteraemia: presence of a positive catheter tip culture (>10³ ufc/mL), associated with secondary bacteremia due to the same bacteria as retrieved from the catheter in the absence of another focus of infection with the same bacteria.
- Catheter infection: presence of a positive culture of the tip of the catheter (>10³ ufc/mL) in
the presence of general or local signs of infection, with at least partial regression of symptoms on removal of the catheter.

2.2 PVC complications
Localised erythema (>2cm from insertion site)
Phlebitis
Unexplained bacteraemia: positive blood culture in the absence of obvious infectious focus.
Catheter-related bacteraemia: presence of a positive catheter tip culture (>10^3 ufc/mL), associated with secondary bacteremia due to the same bacteria as retrieved from the catheter in the absence of another focus of infection with the same bacteria.
Catheter infection: presence of a positive culture of the tip of the catheter (>10^3 ufc/mL) in the presence of general or local signs of infection, with at least partial regression of symptoms on removal of the catheter.

3. Thrombotic complications
3.1 CVC complication
- Complete vein (jugular, femoral or subclavian) thrombosis (ultrasound examination)
3.2 PVC complication
- Deep vein thrombosis (at least 3 cm long upon ultrasound examination)

B) Minor complications
1. Mechanical complications
1.1 During CVC insertion
- Successful insertion after attempts at two different sites
- Successful insertion after three attempts at the same site
- Local haematoma less than 3 cm²
1.2 During PVC insertion
- for a given PVC, necessity to replace the catheter within 24h
- At least two catheter replacements within 24h, or once within 24h two days in a row
- Subcutaneous diffusion < 5x5 cm

2. Infectious complications
2.1 CVC
- Localised erythema (<2cm from insertion site)
- Catheter contamination: presence of a positive culture of the tip of the catheter (but <10^3 ufc/mL), in the absence of general or local signs of infection.
- Catheter colonisation: presence of a positive culture of the tip of the catheter (> 10^3 ufc/mL), in the absence of general signs of infection due to the catheter. Locally, there may be erythema, but without local suppuration. Colonization may come from a remote focus.

2.2 PVC
- Localised erythema (<2cm from insertion site)
- Aseptic cellulitis
- Catheter contamination: presence of a positive culture of the tip of the catheter (but <10^3 ufc/mL), in the absence of general or local signs of infection.
- Catheter colonisation: presence of a positive culture of the tip of the catheter (> 10^3 ufc/mL), in the absence of general signs of infection due to the catheter. Locally, there may be erythema, but without local suppuration. Colonization may come from a remote focus.

3. Thrombotic complications
3.1 CVC complication
- Incomplete vein (jugular, femoral or subclavian) thrombosis (ultrasound examination)

3.2 PVC complication
- Superficial vein thrombosis (at least 3 cm long upon ultrasound examination)
SM 3

Rating of catheter-related complications

There is no validated classification of adverse events in ICU. Therefore we developed two strategies to rate the complications related to venous access.

We defined *a priori* a list of complications (n=42) related either to catheter insertion or to catheter maintenance. These complications were *a priori* defined for both types of catheters as major (n=27) or minor (n=15), taking into account both the potential medical severity and the potential discomfort undergone by patients.

The important limitation to this analysis is that it does not take into account the true outcome of the complication. For example, a pneumothorax is listed as a unique complication, whether it didn’t even require a chest tube or if lead to the patient’s death.

We therefore complemented the study analysis by the use of a validated classification, rating complications according to the actual facts: i.e. the intervention required. We used the Common Terminology Criteria for Adverse Events (CTCAE-V3) classification, which is widely used in cancer clinical trials. We checked that all the complications listed in our research protocol (n=42) were recorded in the CTCAE-V3. We then validated the rating proposed in the classification (grade 1: minimal symptoms, invasive intervention not indicated; grade 2: minimally invasive intervention indicated; grade 3: interventional or operative intervention indicated important intervention; grade 4: life-threatening consequences; major urgent intervention indicated; grade 5: Death). Validation was obtained through a Delphi consensus of 40 senior ICU physicians, all members of the French Society of Intensive Care (SRLF). Consensus was sought both for the appropriateness of the complication’s description and the therapeutic interventions required to treat it and for the rating of the event’s outcome.

The screen capture below illustrates the question regarding the grading of the pneumothorax.
10. Pneumothorax

- grade 1: asymptomatic radiographic findings only
- grade 2: symptomatic; intervention indicated (e.g., hospitalisation for observation, tube placement without sclerosis)
- grade 3: sclerosis and/or operative intervention indicated
- grade 4: life-threatening causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated
- grade 5: death

<table>
<thead>
<tr>
<th>1</th>
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1 total disagreement (1) to 9 total agreement (9)

Commentaires éventuels
Rating of medical and paramedical time spent to manage catheters

We rated the time spent by doctors and nurses to manage central and peripheral catheters using the same philosophy as the Common Terminology Criteria for Adverse Events (CTCAE-V3) classification. The scale is shown below in the tables. It was also validated through the Delphi consensus. The physicians were asked to validate the rating of the following:

- Time spent by medical team for CVC insertion
- Time spent by paramedical team for CVC insertion
- Time spent by paramedical team for PVC insertion.

A number of events were identified: number of attempts, change of site, necessity to replace a PVC in less than 24h, etc. Grade 1 was the least time required and 5 the most.

We questioned the ICU physicians on their agreement towards the labelling of the different events, and also to, on their agreement toward to the grading in terms of time spent.

Physicians expressed their feeling towards the grading from 1 (total disagreement) to 9 (total agreement).

See for example the screen capture of the survey for the time spent by medical team for CVC:

<table>
<thead>
<tr>
<th>1. TIME SPENT BY MEDICAL TEAM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central catheter insertion</strong></td>
</tr>
<tr>
<td>Grade 1: central catheter insertion after failure of peripheral insertion or maintaining peripheral access.</td>
</tr>
<tr>
<td>Central access required</td>
</tr>
<tr>
<td>Grade 2: success with 3 punctures, no change of insertion site</td>
</tr>
<tr>
<td>Grade 3: 1 change of insertion site to succeed initial insertion or to maintain central IV access</td>
</tr>
<tr>
<td>Grade 4: 2 changes of insertion site to succeed initial insertion on third site</td>
</tr>
<tr>
<td>Grade 5: failure of catheter insertion after attempts on at least 2 different sites</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>9</th>
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<tbody>
<tr>
<td>total disagreement (1) to total agreement (9)</td>
<td></td>
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Commentaires éventuels

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Supplemental material - Central or peripheral catheters for initial venous access of ICU patients: a randomized controlled trial
### Time consumption for medical team

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVC insertion difficulties</td>
<td>CVC insertion after failure of peripheral insertion or maintaining peripheral access. Central access required</td>
<td>Success with 3 attempts, no change of insertion site</td>
<td>1 change of insertion site to succeed initial insertion or to maintain central IV access</td>
<td>2 changes of insertion site to succeed initial insertion on third site</td>
<td>Failure of CVC insertion after attempts on at least 2 different sites</td>
</tr>
</tbody>
</table>

### Time consumption for paramedical team

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVC insertion difficulties</td>
<td></td>
<td>Success with 3 attempts, no change of insertion site</td>
<td>1 change of insertion site to succeed initial insertion or to maintain central IV access</td>
<td>2 changes of insertion site to succeed initial insertion on third site</td>
<td>Failure of CVC insertion after attempts on at least 2 different sites</td>
</tr>
<tr>
<td>PVC insertion difficulties</td>
<td>More than 2 attempts required within 24 hours</td>
<td>More than 5 attempts to succeed initial insertion</td>
<td>Failure of PVC insertion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tables describing the grading of the medical and paramedical time consumption required with CVC and PVC insertion difficulties
SM 5

Ethical considerations

Considering that most patients were in no conditions of being informed of the study at the time of inclusion, the ethics committee recommended that, whenever possible, a written informed consent was obtained from the patient or proxies. When the patient was not conscious and proxies were unavailable, the patient was included in the study. During the course of the hospitalisation in ICU, if a satisfactory state of consciousness was restored, the patient’s consent was obtained a posteriori. Patient’s refusal, at any stage of the study, implied his/her retrieval from the study.

The study received the required legal approval from the appropriate French data protection committees (Comité Consultatif pour le Traitement de l’Information en Matière de Recherche dans le Domaine de la Santé, and Commission Nationale Informatique et Liberté), ensuring that patient data were kept confidential according to the French regulation.
SM 6

Time to first major CVC complication

Time to first major CVC complication in patients allocated to receive a CVC was 2.9±5.5 days. This figure was 6.0±6.5 days in patients allocated to initially receive a PVC but that were crossed over to receive a CVC, p=0.08.

SM 7

Attributable complications

<table>
<thead>
<tr>
<th>Mechanical complications</th>
<th>CVC</th>
<th>PVC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>6</td>
<td>0</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Arterial puncture</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PVC insertion difficulties</td>
<td>0</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous diffusion</td>
<td>0</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Change in CVC insertion site</td>
<td>43</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infectious complications</th>
<th></th>
<th></th>
<th>p&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>1</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Phlebitis</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unexplained bacteraemia</td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Catheter-related bacteraemia</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Catheter infection</td>
<td>3</td>
<td>10</td>
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</tbody>
</table>

SM 8

Complication rates according to the common terminology classification for adverse events

A Delphi survey was performed among 40 senior ICU physicians, all members of the French Society of Intensive Care.

Physicians were questioned on two points: 1) did they agree with the grading of the severity for each individual complication?; 2) for a given grade, did they agree with the labelling of each complication.
Physicians had to choose how they felt towards each proposition on a scale from 1 (total disagreement) to 9 (total agreement). A second round was performed when disagreement (1-4) was greater than 50%. This was never the case.
Median agreement (6-9) was 71.9% for the first assessment, and 86.3% for the second.

**SM 9**

**Medical and paramedical resource required for catheter insertion**

Medical and paramedical staff involvement was greater in PVC group compared to CVC group (weighted score: 3·20 v. 1·81 respectively, p<0.0001).