Low concentration of heparin used for permanent catheters canal locking is effective and diminishes the risk of bleeding

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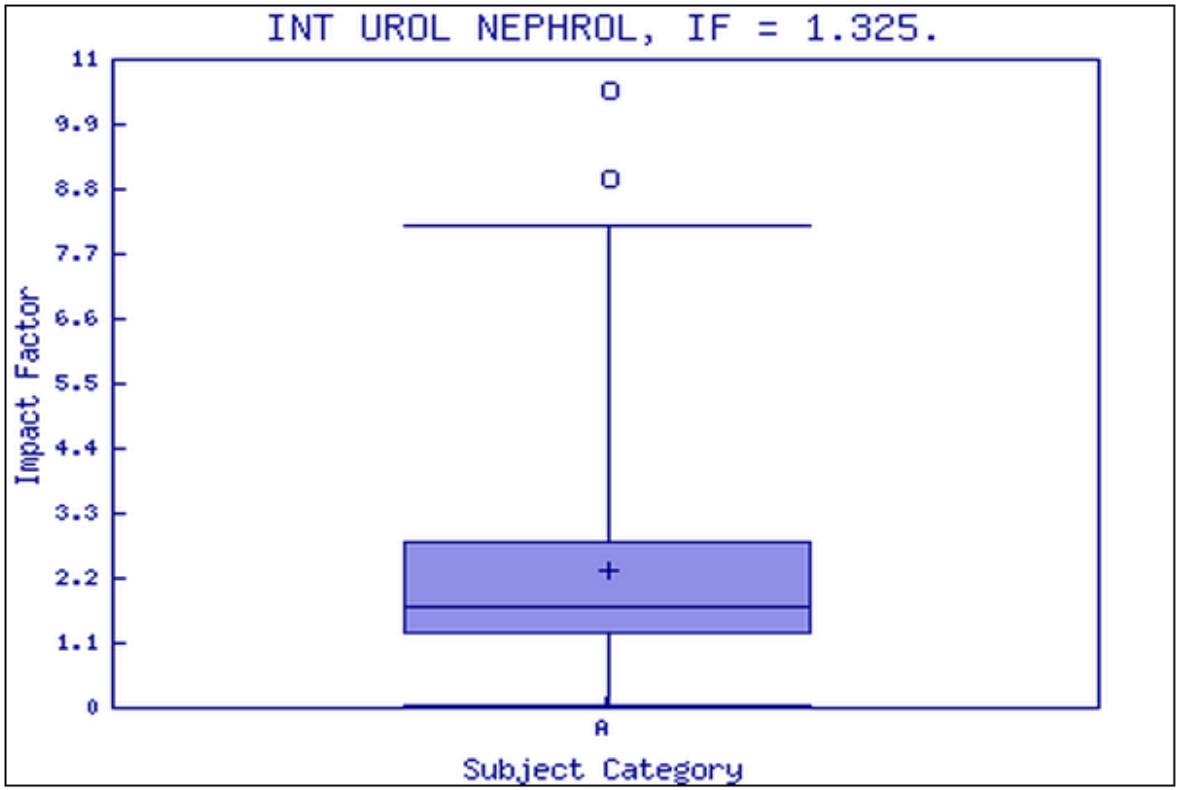
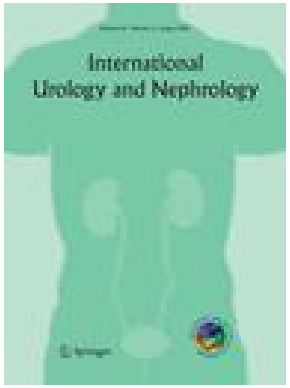
臨床問題

- Perm catheter 留置之洗腎病人
- 本院標準規範：動靜脈端會給予 Heparin 5,000 IU/ML 避免管路阻塞
  - 目前腎臟科醫學會/腎臟護理學會，並無明確的 Guideline

- 但，臨床上發現病人洗腎後較容易有出血傾向?
- 是否與 Heparin 有關?

Journal:
INTERNATIONAL UROLOGY AND NEPHROLOGY





Key

A - UROLOGY & NEPHROLOGY

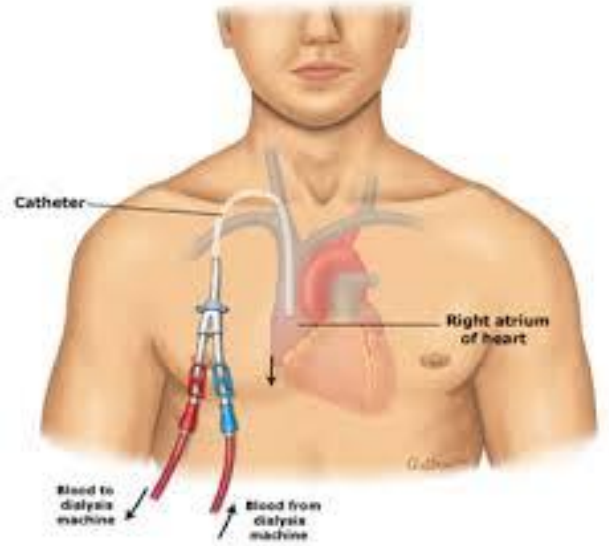
Introduction

- Two viable options exist for hemodialysis patients (HD)
  - Arteriovenous fistula
    - current guidelines unequivocally recommend as the preferred vascular access for HD
  - Central venous catheter

- Up to 80% of HD start renal replacement therapy with a catheter and in 1/3 of them it serves as a long-term vascular access

Introduction

- PC placement associated several complications
  - Cardiac tamponade
  - Pneumothorax
  - Bleeding



  - **Clotting**
  - The concentration of heparin instilled into PC canals varies *from 1,000 to 10,000 IU/ml*, as there are no guidelines addressing this problem.

步驟 1：研究探討的問題為何？

- Population/Problem
  - Patients receiving hemodialysis with central venous catheters.
- Intervention
  - low concentration of heparin, LCH (2,500 IU/ml)
- Comparison
  - high concentration of heparin, HCH (5,000 IU/ml)
- Outcomes
  - The primary endpoint was the occurrence of bleeding within 24 h after catheter placement.
  - The effects of clinical and laboratory data on bleeding events were analyzed as secondary endpoints.

步驟 2：
研究的品質有多好(內在效度)？

招募(Recruitment) - 受試者是否具有代表性？

- Single-center, prospective, randomized, open-label trial
- All patients received dual lumen cuffed catheters
- Before entering the study, all patients gave informed consent.
  - The study was conducted in accordance with the principles of the Declaration of Helsinki.
  - The research protocol was reviewed and accepted by a local ethics committee.

評讀結果:☑是☐否☐不清楚

步驟 2：
研究的品質有多好(內在效度)？

- 分派(Allocation) -
  分派方式是否隨機且具隱匿性？

- Patients were randomized with toss a coin method into one of two groups (LCH vs. HCH), which differed in concentration of heparin used for catheter lumens locking.
- Open-label trial

評讀結果:□是□否☑不清楚

步驟 2：
研究的品質有多好(內在效度)？
每個組別，在研究開始的情況是否相同？

Table 1 Characteristic of two analyzed groups

	LCH	HCH
Subjects (*n*)	37	38
Female/male	18/19	21/17
DM (*n*; %)	9; 24	8; 21
Cause of catheter insertion: incident/prevalent renal failure	10/27	12/26
Age (years)	64 ± 15	65 ± 14
ASA (*n*; %)	10; 28	9; 26
LMWH (*n*; %)	3; 8	3; 8
HGB (g/dl)	10.2 ± 1.9	10.3 ± 1.8
PLT ($\times 10^3$/μl)	215.1 ± 67.5	215.3 ± 99.4
FBG (mg/dl)	431.7 ± 200.7	424.7 ± 203.4
APTT (s)	38.8 ± 5.9	38.9 ± 5.3
INR	1.09 ± 0.11	1.08 ± 0.11

At baseline, both groups did not differ significantly in any of evaluated parameters.

APTT activated partial thromboplastin time, *ASA* use of acetylsalicylic acid, *FBG* fibrinogen, *HCH* high concentration of heparin, *HGB* hemoglobin, *INR* international normalized ratio, *LCH* low concentration of heparin, *LMWH* use of low molecular weight heparin, *PLT* platelet count

評讀結果:☑是☐否☐不清楚

步驟 2：
研究的品質有多好(內在效度)？

維持(maintance)-各組是否給予相同治療?

- All patients received dual lumen cuffed catheters (Covidien Palindrome, Mansfield, MA, USA).
- The catheter insertion took place in a separate room, under aseptic conditions and local anesthesia (1% lidocaine).
- The site of insertion was based on clinical factors and was left to the operator’ s decision.
- Catheters 14.5 Fr/28 cm in length were placed in the internal jugular vein or 14.5 Fr/55 cm when femoral vein was used.
- Immediately after catheter placement, *its patency was checked and lumens were filled with nominal volume of heparin at a concentration in accordance with the assigned group.*
- The correct localization of the catheter was confirmed with X-ray.

評讀結果:☑是☐否☐不清楚

步驟 2：
研究的品質有多好(內在效度)？

是否有足夠的追蹤？

- 75 patients were enrolled in the study
  - ✓ LCH (n = 37)
  - ✓ HCH (n = 38)

- Follow up?
- ITT?

評讀結果: □是□否☑不清楚

步驟 2：
研究的品質有多好(內在效度)？

評估(Measurement)

受試者與評估者是否對治療方式或評估目的維持盲法？

- Open-label trial
- Before catheter placement, WBC and platelet, HGB, fibrinogen concentration, international normalized ratio (INR), and APTT time were measured with ***standard laboratory methods***.
- Two hours after the procedure, APTT was determined.
- All patients were observed for 24 h.

- BLIND? – Researcher, Assessor…

評讀結果:□是☑否□不清楚

步驟 3：
研究結果的意義為何？

使用何種評估方式，療效有多大

- Independent or dependent continuous variables were compared with an appropriate variant of Student *t* test.
- Differences between categorical data were evaluated with $\chi 2$ test.
- For bivariate associations between bleeding episodes and variables of interest, logistic regression analysis was used.
- The variables associated with endpoint in univariate analysis ($p < 0.1$) were included into multivariate logistic regression analysis.

評讀結果: ☑是☐否☐不清楚

步驟 3：
研究結果的意義為何？
這個研究結果是否可能隨機發生[1]？

Table 2 Results of univariate logistic regression analysis

Univariate analysis			
Variable	OR	95% CI	*p*
Sex	1.27	0.47–3.46	0.63
Age	1.01	0.97–1.05	0.60
Indication for catheter insertion: incident/prevalent renal failure	0.79	0.25–2.53	0.69
ASA use	0.95	0.30–3.04	0.93
LMWH use	5.26	0.86–32.09	0.07
HCH group assignment	3.12	1.08–9.02	0.03
Femoral localization	3.32	0.88–12.57	0.07
Side of catheter insertion	1.33	0.35–4.99	0.67
HGB	1.10	0.83–1.44	0.50
PLT	1.00	0.99–1.01	0.88
FBG	1.00	0.99–1.00	0.15
Baseline APTT	1.13	1.02–1.25	0.02
Baseline INR	0.46	0.01–39.74	0.73
APTT 2 h after catheter insertion	1.03	1.01–1.05	0.002

APTT activated partial thromboplastin time, *ASA* use of acetylsalicylic acid, *CI* confidence interval, *FBG* fibrinogen, *HCH* high concentration of heparin, *HGB* hemoglobin, *INR* international normalized ratio, *LMWH* use of low molecular weight heparin, *OR* odds ratio, *PLT* platelet count

步驟 3：
研究結果的意義為何？
這個研究結果是否可能隨機發生[2]？

Table 3 Results of multivariate analysis

Variable	OR	95% CI	*p*
Model 1 $\chi^2 = 16.85$; $p = 0.002$			
HCH assignment	3.64	1.10–12.05	0.03
Baseline APTT	1.12	1.002–1.250	0.04
LMWH use	5.94	0.82–42.88	0.07
Femoral localization	3.12	0.73–13.32	0.12
Model 2 $\chi^2 = 19.86$; $p = 0.0005$			
APTT 2 h after catheter insertion	1.03	1.01–1.06	0.01
Baseline APTT	1.10	0.99–1.23	0.07
LMWH use	4.38	0.61–31.55	0.14
Femoral localization	0.72	0.09–5.62	0.75

Model 1 included use of LMWH, site of catheter placement, baseline APTT value, and group assignment.

Model 2 included instead of group assignment value of APTT 2 h after catheter insertion

結果

HCH high concentration of heparin
LCH low concentration of heparin

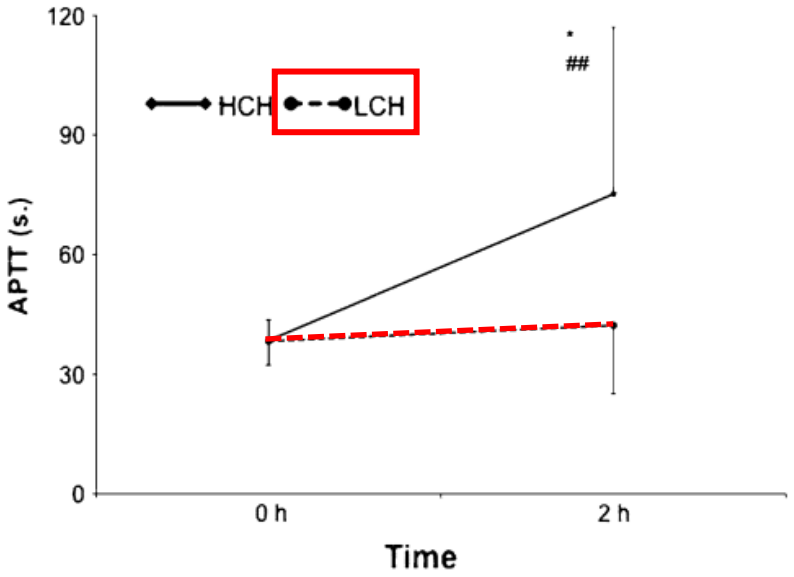


Fig. 1 APTT values with regard to heparin concentration used for catheter canal locking. (*Baseline APTT vs. APTT 2 h after catheter insertion $p < 0.001$, ##comparison of APTT 2 h after catheter insertion HCH vs. LCH $p < 0.001$). *APTT* activated partial thromboplastin time, *HCH* high concentration of heparin, *LCH* low concentration of heparin

jugular vein vs. femoral vein

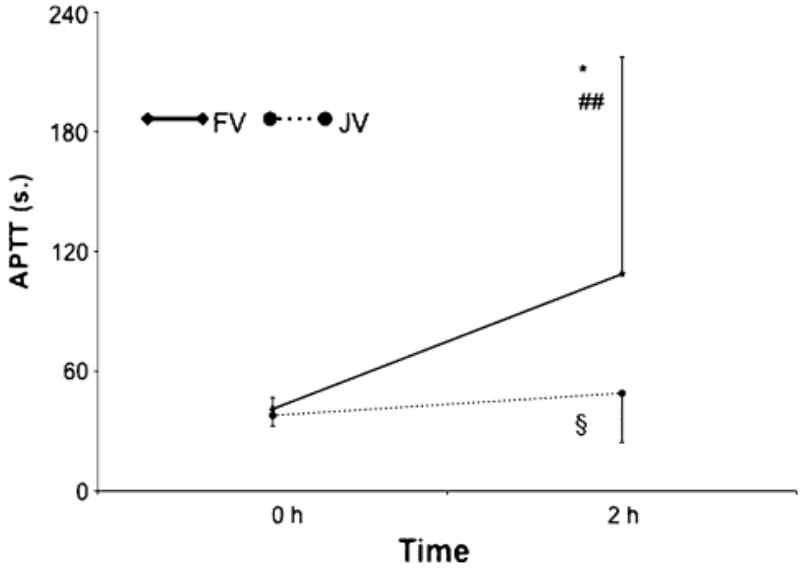


Fig. 2 APTT values with regard to the length of catheter used (*Baseline APTT vs. APTT 2 h after catheter insertion in FV $p < 0.01$, §baseline APTT vs. APTT 2 h after catheter insertion in JV $p < 0.01$, ##comparison of APTT 2 h after catheter insertion FV vs. JV $p < 0.001$) *APTT* activated partial thromboplastin time, *JV* jugular vein, *FV* femoral vein

Locking of permanent catheters lumens with heparin at 2,500 IU/ml when compared to 5,000 IU/ml decreases the risk of bleeding complications in the post surgery period without compromising their patency.

討論及建議事項[1]

提案

- 雙腔導管透析護理技術準則，是否可修訂 Heparin 劑量為 2,500 IU/Ml

決議

- 與會人員共計25人
- 4人 反對
- 13人 懷疑

  (建議應再搜尋更多相關文獻)
- 5人 同意

討論及建議事項[2]

- 文獻
  - ✓缺乏盲化、樣本數少、非ITT... 結果易有偏誤
  - ✓以擲銅板的方式進行隨機化，兩組個案數不多、但收案人數及基本資料卻十分平衡?
  - ✓僅探討導管植入24小時內出血率，未考量其他與導管阻塞之相關因素，如植入部位、推 Heparin 的時間...等。
  - ✓文獻納入之個案數有限，統計方式可能有偏差(是否符合迴歸分析之統計假設?)。
- 臨床建議
  - ✓建議可先調查透析導管植入後出血率及阻塞率，確認問題點。
  - ✓ ICU病人因病況複雜，建議可先由門診洗腎病人逐步進行劑量之調整。

敬請指教