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Prognostic significance of early urinary catheterization after acute stroke: Secondary analyses of the international HeadPoST trial

Menglu Ouyang[1,2], Laurent Billot[1], Lili Song[1,2], Xia Wang[1], Christine Roffe[3], Hisatomi Arima[1,4], Pablo M Lavados[5], Maree L Hackett[1,6], Verónica V Olavarría[5], Paula Muñoz-Venturelli[1,7], Sandy Middleton[8], Octavio M Pontes-Neto[9], Tsong-Hai Lee[10], Caroline L Watkins[6], Thompson G Robinson[11] and Craig S Anderson[1,2,7,12,13]

Abstract

Background: An indwelling urinary catheter (IUC) is often inserted to manage bladder dysfunction, but its impact on prognosis is uncertain. We aimed to determine the association of IUC use on clinical outcomes after acute stroke in the international, multi-center, cluster crossover, Head Positioning in Acute Stroke Trial (HeadPoST).

Methods: Data were analyzed on HeadPoST participants (n = 11,093) randomly allocated to the lying-flat or sitting-up head position. Binomial, logistic regression, hierarchical mixed models were used to determine associations of early insertion of IUC within seven days post-randomization and outcomes of death or disability (defined as "poor outcome," scores 3–6 on the modified Rankin scale) and any urinary tract infection at 90 days with adjustment of baseline and post-randomization management covariates.

Results: Overall, 1167 (12%) patients had an IUC, but the frequency and duration of use varied widely across patients in different regions. IUC use was more frequent in older patients, and those with vascular comorbidity, greater initial neurological impairment (on the National Institutes of Health Stroke Scale), and intracerebral hemorrhage as the underlying stroke type. IUC use was independently associated with poor outcome (adjusted odds ratio (aOR): 1.40, 95% confidence interval (CI): 1.13–1.74), but not with urinary tract infection after adjustment for antibiotic treatment and stroke severity at hospital separation (aOR: 1.13, 95% CI: 0.59–2.18). The number exposed to IUC for poor outcome was 13.

Conclusions: IUC use is associated with a poor outcome after acute stroke. Further studies are required to inform appropriate use of IUC.

[1]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia
[2]The George Institute China at Peking University Health Science Center, Beijing, China
[3]Department of Neurosciences, Royal Stoke University Hospital, Stoke-on-Trent, UK
[4]Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan
[5]Departmento de Neurologia and Psiquiatria, Clínica Alemana de Santiago, Servicio de Neurología, Unidad de Neurología Vascular, Vitacura, Chile
[6]Faculty of Health and Wellbeing, University of Central Lancashire, Preston, Lancashire, UK
[7]Center for Clinical Studies, School of Medicine—Clínica Alemana, ICIM, Universidad del Desarrollo, Santiago, Chile
[8]Nursing Research Institute, St Vincent's Health Australia, Australian Catholic University, Sydney, Australia
[9]Stroke Service—Neurology Division, Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, University of Sao Paulo, Ribeirão Preto, Brazil
[10]Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taoyuan
[11]Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK
[12]Neurology Department, Royal Prince Alfred Hospital, Sydney Health Partners, Sydney, Australia
[13]Heart Health Research Center, Beijing, China

Corresponding author:
Craig S Anderson, The George Institute for Global Health, PO Box M201, Missenden Rd., Sydney, NSW 2050, Australia.
Email: canderson@georgeinstitute.org.au

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Bladder dysfunction is common after acute stroke, affecting at least one third of patients.[1] A urodynamic study suggested frequencies of urinary incontinence of 73% and 64%, and urinary retention of 13% and 52%, in patients with acute intracerebral hemorrhage (ICH) and ischemic stroke, respectively.[2] An indwelling urine catheter (IUC) is often inserted to manage these conditions,[3] but the benefits may be offset by increased mortality and morbidity, especially in the context of incontinence.[4,5] Guidelines[6,7] therefore recommend cautious use of IUC and for their early removal to avoid urinary tract infection (UTI) and other sepsis. However, these recommendations are based on level C grade of evidence, since the data are derived from studies limited by small sample size, retrospective design, and incomplete adjustment for confounding. We aimed to determine associations of IUC use and 90-day clinical outcomes in stroke patients with a broad range of characteristics who participated in the international Head Positioning in Acute Stroke Trial (HeadPoST).[8]

Methods

Study population

HeadPoST was an international, multicenter, cluster crossover, clinical trial that involved 11,093 adults (≥18 years) with acute stroke randomly allocated to the lying flat or sitting up head position soon at 114 hospitals in nine countries from March 2015 to November 2016.[8] A guardian consent process was used to implement the randomized intervention as a policy of usual service delivery to a pre-defined patient cluster; patients provided consent for use of their medical record data and centralized telephone follow-up. HeadPoST is registered at ClinicalTrials.gov (NCT02162017).

Procedures

Demographic, medical history, and clinical information, included the severity of neurological impairment on the National Institutes of Health Stroke Scale (NIHSS), were collected at baseline. Data of IUC use, including insertion date, along with other pre-defined management interventions, repeat NIHSS, and an assessment of functional status on the simplified modified Rankin scale (mRS) were collected at day 7 post-randomization (or at hospital separation if earlier). Recorded IUC use was assumed as the first insertion after hospital admission and duration of use was censored at day 7. Trained staff, blind to treatment allocation, contacted patients not known to have died by telephone to assess their functional status on the mRS at 90 days. The primary outcome for these analyses was death or dependency (mRS scores 3–6). The secondary outcome was UTI identified from details related to serious adverse events (SAEs) reported by site investigators to the end of follow-up at 90 days.[8]

Statistical analysis

Binomial, logistic regression, hierarchical mixed models were used to adjust for the fixed effects of head position (lying-flat vs. sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period. The term "unadjusted" was used for convenience in defining this initial mixed model. Potential confounders at baseline and day 7 post-randomization (P value < 0.2) in univariate analyses (Table 1; Supplemental Tables S1 and S2) defining associations of IUC and outcomes were included in sequential hierarchical logistic regression models with (model I) country groups according to region, (model II) baseline characteristics, and (model III) management covariates. As the NIHSS and mRS scores at day 7 (or earlier) were correlated (Spearman's rank correlation $= 0.72$), the former scale was used in model III to adjust for early neurological change. As there was a high proportion of missing day 90 mRS scores (12%), multiple imputation was conducted for a sensitivity analysis with all covariates (include outcome variable) in the mixed model for analysis (method was described in Supplemental Material). Considering UTI as an intermediate variable for IUC and poor functional outcome, an additional sensitivity analysis was conducted to assess the strength of association in patients without UTI. Pre-specified subgroup analyzes considered head position, age, sex, baseline neurological severity (NIHSS score), and medical history. To assist in understanding the adverse consequences of IUC use, we calculated a number needed to expose for poor outcome using the adjusted odds

Table 1. Characteristics of 11,093 patients by urinary catheter use

Characteristics	Urinary catheter inserted		P value[a]
	Yes (N = 1167)	No (N = 9829)	
Age, years	71.3 ± 13.9	67.5 ± 13.7	<0.0001
Male	610 (52.3)	5999 (61.0)	<0.0001
Region			<0.0001
Australia/UK	535 (45.8)	4154 (42.3)	
China (incl. Taiwan)	266 (22.8)	4371 (44.5)	
India/Sri Lanka	259 (22.2)	507 (5.2)	
South America	107 (9.2)	797 (8.1)	
Hypertension	630 (54.0)	4948 (50.3)	0.140
Previous stroke	272 (23.3)	2314 (23.5)	0.854
Coronary artery disease	192 (16.5)	1337 (13.6)	0.008
Atrial fibrillation	227 (19.5)	936 (9.5)	<0.0001
Heart failure	70 (6.0)	337 (3.4)	<0.0001
Diabetes mellitus	252 (21.6)	1956 (20.0)	0.642
Stroke category			<0.0001
AIS	950 (81.5)	8442 (86.1)	
ICH	192 (16.5)	728 (7.4)	
Uncertain	24 (2.1)	637 (6.5)	
NIHSS at admission	12.0 (6.0, 18.0)	4.0 (2.0, 7.0)	<0.0001
GCS score at admission	14.0 (11.0, 15.0)	15.0 (14.0, 15.0)	<0.0001
Pre-morbid mRS 0–1[b]	881 (75.5)	7782 (79.2)	0.008
NIHSS at 7 days	9.0 (4.0, 16.0)	2.0 (1.0, 5.0)	<0.0001
mRS at 7 days	4.0 (3.0, 5.0)	2.0 (1.0, 3.0)	<0.0001
ICU admission	242 (20.7)	274 (2.8)	<0.0001
ASU admission	824 (70.6)	5716 (58.2)	<0.0001
Antibiotic treatment	526 (45.1)	1146 (11.7)	<0.0001
Underwent surgery[c]	29 (2.5)	7 (0.1)	<0.0001

Note: Data are n (%), mean (SD) and median (IQR). AIS: acute ischaemic stroke; SD: standard deviation; IQR: interquartile range; ASU: acute stroke unit; GCS: Glasgow coma scale; ICH: intracerebral hemorrhage; ICU: intensive care unit; mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale.

[a]P values from the Student's t-test or Wilcoxon rank-sum test for continuous variables, and the Chi-squared test or Fisher's extract test for categorical variables.

[b]Estimated functional grade score 0–1 on the mRS.

[c]Includes decompressive hemicraniectomy, open craniotomy, minimally invasive surgery, and intraventricular drainage of ICH.

ratio (aOR) obtained in models.[9] Data are reported with 95% confidence intervals (CIs), and a two-sided $P < 0.05$ was considered statistically significant. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC).

Data sharing

Individual participant data used in these analyses can be shared by formal request with protocol from any qualified investigator to the Research Office of The George Institute for Global Health, Australia.

Results

Patient characteristics for IUC insertion

Of the 11,093 randomized HeadPoST patients (mean age 68 ± 14 years; 60% male), 1167 (11.6%) had an IUC inserted during their hospitalization, but this figure varied widely across regions: highest for participants in India/Sri Lanka (33.8%), followed in decreasing frequency by those in South America, Australia/UK, and China (including Taiwan) (Supplemental Table S3). The median duration over seven days of IUC insertion was five days (interquartile range (IQR): 3–7) (Supplemental Table S3).

Table 1 shows that the highest likelihood of IUC use was in older patients, and those with history of heart disease, greater initial neurological impairment, and a diagnosis of ICH. In particular, most (70.7%) older patients ($\geq$65 years) had an IUC. Similarly, day 7 data indicate that IUC use was related to greater neurological impairment and physical disability, defined by higher NIHSS and mRS scores, respectively. Moreover, IUC use was more frequent after an admission to an intensive care or acute stroke unit, and in those who received antibiotics within the seven days, as compared to those without an IUC (Table 1).

IUC and outcomes

Median duration of IUC use in patients with a poor outcome (death or dependency, mRS 3–6) was significantly higher than in those with good functional recovery (six vs. five days, $P = 0.013$; Supplemental Table S4). Compared to patients without an IUC, those with IUC had a greater likelihood of a poor outcome (76.6% vs. 34.7%; $P < 0.0001$; Supplemental Table S5). Table 2 shows that the increased odds of poor outcome with IUC use persisted after adjustment for imbalance in baseline characteristics and post-randomization management variables (model III aOR: 1.40, 95% CI: 1.13–1.74) and after multiple imputation of missing outcome data (aOR: 1.36, 95% CI: 1.14–1.63). A significant interaction was found for IUC use and baseline NIHSS score (P for interaction 0.0019; Supplemental Figure S1). The number needed to be exposed to an IUC for harm (death or dependency) was 13.

Overall, only 0.7% (76/11,093) patients had a UTI (Supplemental Table S5), and this was more likely in those with IUC (1.5% vs. 0.6%, $P = 0.0002$; Supplemental Table S5). The median time to diagnosis of UTI was 17 (IQR: 5–36) days; but only 38% (29/76) of UTI events occurred within day 7/discharge (Supplemental Figure S2). However, in those patients

Table 2. Association of urinary catheter use and death or dependency at 90 days

Model	Complete case dataset		Multiple imputation dataset	
	aOR (95% CI)	P value	aOR (95% CI)	P value
Unadjusted[a]	5.44 (4.54–6.39)	<0.0001	5.17 (4.44–6.02)	<0.0001
Model I[b]	5.27 (4.49–6.18)	<0.0001	5.01 (4.31–5.83)	<0.0001
Model II[c]	2.31 (1.91–2.78)	<0.0001	2.21 (1.85–2.64)	<0.0001
Model III[d]	1.40 (1.13–1.74)	0.002	1.36 (1.14–1.63)	0.001

aOR: adjusted odds ratio; CI: confidence interval.

[a]Binomial logistic regression model with adjustment for the fixed effects of head position (lying-flat vs. sitting-up) and crossover period, and random effects of cluster, and random interaction effects between cluster and crossover period.

[b]Model I adjusted for region (Australia/UK, China including Taiwan, India/Sri Lanka, South America).

[c]Model II is model I with further adjustment for baseline covariates of age as a continuous variable, sex, estimated premorbid grade 0 or 1 on the mRS, baseline NIHSS score as a continuous variable, history of heart disease (any heart failure, atrial fibrillation or coronary artery disease), diabetes mellitus or stroke, and pathological stroke type.

[d]Model III is model II further adjusted for individual variables at day 7 or earlier hospital separation, including intensive care unit admission, acute stroke unit admission, antibiotic use, and NIHSS score as a continuous variable.

Table 3. Association of urinary catheter use and urinary tract infection within 90 days

Model	Original dataset		Multiple imputation	
	aOR (95% CI)	P value	aOR (95% CI)	P value
Unadjusted[a]	2.85 (1.62–4.99)	0.0003	2.85 (1.62–4.99)	0.0003
Model I[b]	2.58 (1.47–4.53)	0.001	2.58 (1.47–4.53)	0.001
Model II[c]	2.08 (1.13–3.82)	0.018	2.05 (1.12–3.75)	0.020
Model III[d]	1.13 (0.59–2.18)	0.707	1.18 (0.63–2.19)	0.610

aOR: adjusted odds ratio; CI: confidence interval.
[a]Binomial logistic regression model with adjustment for the fixed effects of head position (lying-flat vs. sitting-up) and crossover period, and random effects of cluster, and random interaction effects between cluster and crossover period.
[b]Model I adjusted for region (Australia/UK, China including Taiwan, India/Sri Lanka, and South America).
[c]Model II is model I with further adjustment for baseline covariates of age as a continuous variable, sex, estimated premorbid grade 0 or 1 on the mRS, baseline NIHSS score as a continuous variable, history of heart disease (any heart failure, atrial fibrillation or coronary artery disease), diabetes mellitus or stroke, and pathological stroke type.
[d]Model III is model II further adjusted for individual variables at day 7 or earlier hospital separation, including intensive care unit admission, acute stroke unit admission, antibiotic use, and NIHSS score as a continuous variable.

with UTI, there was no clear difference in the median duration of IUC compared to those without UTI (4 (3–6) vs. 5 (3–7) days; $P = 0.17$) (Supplemental Table S4). Table 3 shows this association in the initial adjusted analysis (model II, aOR: 2.08, 95% CI: 1.13–3.82), but lost significance after adjustment for post-randomization management variables that included antibiotic use and day 7 (or hospital discharge) neurological severity (model III, aOR: 1.13, 95% CI: 0.59–2.18). These associations remained after multiple imputation (model III, OR: 1.18, 95% CI: 0.63–2.19). In patients who received an IUC, duration of early use was not associated poor outcome (aOR: 1.03, 95% CI: 0.93–1.14; Supplemental Table S6).

Subgroup analysis

The odds of poor outcome being higher in females (P for interaction 0.01), the elderly (age > 80 years; P for interaction 0.006), and those with mild neurological impairment (NIHSS scores of 0–4; P for interaction < 0.0001) compared in other subgroups (Supplemental Figure S3). No heterogeneity was found for stroke subtypes (P for interaction 0.47; Supplemental Figure S3), nor among subgroups for outcome in those with UTI (Supplemental Figure S4).

Role of UTI on poor outcome

Patients with UTI were more likely to have a poor 90-day outcome compared to those without UTI (71.9% vs. 39.0%; $P < 0.0001$; Supplemental Table S2), but not after adjusting for all confounders (aOR: 1.46, 95% CI: 0.70–3.04; Supplemental Table S7). The positive association of IUC and poor outcome persistent after including UTI as a confounder in the primary analysis (aOR: 1.41, 95% CI: 1.13–1.75; Supplemental Table S7). Sensitivity analysis shows that the positive association of IUC use and poor outcome was also present in patients without UTI, and of the same magnitude as identified in the primary analysis of the overall population (aOR: 1.43, 95% CI: 1.15–1.78; Supplemental Table S8).

Discussion

In these secondary analyses of a large population of patients with acute stroke, we have shown that inserting an IUC was associated with a poor functional outcome after adjusting for various prognostic and management confounders, including a diagnosis of UTI and early in-hospital antibiotic use.

Overall, approximately 1 in 10 stroke patients in our study had an IUC inserted, but the frequency was higher in the elderly and those with a history of heart disease, greater baseline neurological deficit, and ICH as the cause. As such, the lower overall frequency of IUC in our study than reported in registries (20%–30%)[4,5,10] may reflect the selective nature of the clinical trial population which included patients with predominantly mild to moderate neurological severity, despite the pragmatic design and broad inclusion criteria. Yet, our data are consistent with others in showing an association of IUC with increasing age and stroke severity.[4,11] Clearly, critical ill patients with more severe deficits are at increased risk of bladder dysfunction and adverse outcomes, and therefore, they require more intensive monitoring and interventional procedures, such as IUC insertion.

Explanations for the adverse consequences of IUC insertion not so clear cut.[5] While an IUC may compromise early mobilization and rehabilitation and cause an inflammatory reaction from subclinical urosepsis.[12] Another explanation for the significant association of IUC and poor outcome is indication bias, whereby patients at risk of poor recovery (old age or severe disability) are more likely to receive an IUC as part of their management. Our subgroup analyses showed the adverse effect of IUC to be greater in patients with mild deficits (NIHSS scores 0–4) and early residual disability (mRS 0–2), suggesting caution in considering an IUC in such patients. Protocols outlining indications and management of IUC may help reduce complications and improve outcomes.[13,14] Moreover, the finding elsewhere of females with poor functional stroke outcome[15] having higher rates of inappropriate IUC use[16] may explain our finding of sex differences in the prognostic significance of IUC.

A recent meta-analysis has shown a wide frequency (3%–44%) of UTI after stroke according to study design and setting.[17] Once again, the low (0.7%) frequency of UTI in HeadPoST compared to an observational study[18] may relate to selection and observer bias, and diagnosis based on reported SAEs rather than systematic surveillance. However, our approach was arguably more clinically relevant in using a "clinically significant" endpoint and in showing attenuation of the association of IUC use and UTI after adjustment for antibiotic use and level of functional impairment. Our findings are therefore contrary to a previous hospital-based study showing a significant association of IUC and UTI,[19] but these results were based on small sample where UTIs were reported without standard diagnostic criteria, and there was no adjustment for other variables, such as antibiotic use. Our study also contrasts with another study which found an association of UTI and poor functional outcome (mRS 3–5) at the time of hospital discharge,[20] but is consistent with another study where adjustments were made for prognostic covariates.[5] Nonetheless, we recognize that the small number of cases of UTI in our study restricted our ability to undertake stratified analyzes or adjust for a large number of covariates.

Strengths of our study include the large sample size of participants with a broad range of characteristics managed in a range of health-care settings. Moreover, we were able to adjust for a large number of potential confounding prognostic factors in different multivariable models. However, in any observational study, there is the potential for incomplete adjustment, while the lack of systematic screening for UTI and reliance on SAE data, likely biased reported events toward those that were more clinically significant or symptomatic. We also had very limited information of the type of IUCs used, their indication, timing of removal, and relationship in the use of antibiotics. The data of censored assessment of all hospital management also limited the utility analysis of IUC duration and outcomes.

In summary, IUC use is associated with a poor functional outcome after acute stroke, after adjustment for a range of important prognostic and management factors. Further studies are required to establish causal pathways and inform guideline recommendations regarding the appropriate indications for IUC to decreases potential risks and promote recovery in vulnerable patients.

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Author contributions

CSA and MO contributed to the concept and rationale for the study. MO undertook statistical analyses with assist from LB. MO wrote the first draft of manuscript with input from CSA. All authors commented upon and approved the final version of the manuscript for publication.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MLH holds a National Health and Medical Research Council of Australia (NHMRC) Career Development Fellowship. SM was a member of the NHMRC Research Committee during 2015–2018. TGR is a senior investigator at National Institutes for Health Research (NIHR). CSA holds an NHMRC Senior Principal Research Fellowship and reports honoraria and travel reimbursement from Takeda, Boehringer Ingelheim, and Amgen outside of this study. The other authors have no disclosures to report.

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ORCID iDs

Menglu Ouyang https://orcid.org/0000-0001-7917-6858
Laurent Billot https://orcid.org/0000-0002-4975-9793
Xia Wang https://orcid.org/0000-0002-1684-7076
Maree L Hackett https://orcid.org/0000-0003-1211-9087
Verónica V Olavarría https://orcid.org/0000-0003-4300-9921
Sandy Middleton https://orcid.org/0000-0002-7201-4394
Craig S Anderson https://orcid.org/0000-0002-7248-4863

Supplemental material

Supplemental material for this article is available online.

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