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REPRESENTATIVENESS OF HONEYPOT TRIAL PARTICIPANTS TO AUSTRALASIAN PD PATIENTS

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♦ ***Background:*** **The HONEYPOT trial failed to establish the superiority of exit-site application of Medihoney compared with nasal mupirocin prophylaxis for the prevention of peritonitis in peritoneal dialysis (PD) patients. This study aimed to assess the representativeness of the patients in the HONEYPOT trial to the Australian and New Zealand PD population.**

♦ ***Methods:*** **This study compared baseline characteristics of the 371 PD patients in the HONEYPOT trial with those of 6,085 PD patients recorded on the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry.**

♦ ***Results:*** **Compared with the PD population, the HONEYPOT sample was older (standardized difference [*d*] = 0.19, $p = 0.003$), more likely to be treated with automated PD ($d = 0.58$, $p < 0.001$), had higher residual renal function ($d = 0.26$, $p < 0.001$) and a higher proportion of participants with end-stage kidney disease due to polycystic kidney disease ($d = 0.17$) and lower proportion due to diabetes ($d = -0.17$) and glomerulonephritis ($d = -0.18$) ($p < 0.001$), and lower proportions of indigenous people ($d = -0.17$, $p < 0.001$), current smokers ($d = -0.10$, $p < 0.001$), and people with prior histories of hemodialysis ($d = -0.16$, $p < 0.001$), diabetes mellitus ($d = -0.18$, $p < 0.001$), and coronary artery disease ($d = -0.15$, $p < 0.001$).**

♦ ***Conclusions:*** **HONEYPOT trial participants tended to be healthier than the Australian and New Zealand PD patient population. Although the differences between the groups were generally modest, it is possible that their cumulative effect may have had some impact on external generalizability, which is not an uncommon occurrence in clinical trials.**

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Recurrent or severe exit-site infections (ESI) and peritonitis are serious complications of peritoneal dialysis (PD) and are associated with increased risks of catheter removal and PD technique failure (1,2). Topical application of mupirocin at either the exit site or intranasally has been recommended in the International Society for Peritoneal Dialysis (ISPD) guidelines (3) for prophylaxis against PD-related infections. However, the agent has been found to be ineffective at preventing gram-negative PD-related infections (4). Furthermore, there is an increasing number of reports indicating that widespread use of mupirocin leads to the development of resistant organisms (5,6). Over the past few decades, the application of honey as an infection prevention agent has been increasingly advocated on the basis of its broad-spectrum antibacterial coverage, particularly against multi-resistant organisms (7–10), as well as the fact that it does not induce antimicrobial resistance (8).

Recently, the HONEYPOT study (11), a multi-center, multinational randomized controlled trial (RCT), including patients from 26 centers in Australia and New Zealand between 2008 and 2011, reported that daily exit-site application of antibacterial honey was not superior to nasal mupirocin prophylaxis for preventing overall PD-related infection (12) or organism-specific peritonitis (13). Honey increased the rates of peritonitis in participants with diabetes mellitus and resulted in a relatively high withdrawal rate due to local skin reactions (6%). The trial findings suggested that honey should not replace mupirocin as the prophylactic standard for PD-related infections.

Whilst clinical trialists, research funding bodies, regulatory agencies, and medical journals devote considerable attention to the internal validity of RCTs like the HONEYPOT trial, their external validity (or generalizability) is frequently overlooked even though this aspect is critically important to adequately informing treatment decisions made by doctors and patients. For example, many RCTs typically enroll less than 60% of screened patients (14), less than 10% of eligible patients per study center (15), and less than 0.5% of the total target population (15). In order to aid doctors and patients in determining the applicability of the HONEYPOT trial's findings to "real-life" clinical practice, it is important to determine how representative the HONEYPOT trial participants were of the broader PD patient populations in Australia and New Zealand, particularly with respect to characteristics that have been shown to influence the risk of PD-related peritonitis, such as demographic factors (e.g. age, gender, ethnicity) (16), current smoking status (17), comorbidities (18–20), body size (18), poor residual kidney function (21), prior hemodialysis (22), and PD treatment characteristics (23,24). This study compared the baseline demographic characteristics, comorbidities and PD parameters of HONEYPOT trial participants with the population of PD patients in Australia and New Zealand during the trial recruitment period, as recorded by the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry.

MATERIALS AND METHODS

STUDY DESIGN

This was a retrospective, cross-sectional observational study designed to compare baseline characteristics of the HONEYPOT trial sample with those patients in Australia and New Zealand who were receiving PD and were recorded on the ANZDATA Registry during the trial recruitment period (17 September 2008 to 17 June 2011).

STUDY POPULATION

The HONEYPOT study aimed to recruit 370 PD patients from PD units throughout Australia and New Zealand. The HONEYPOT inclusion criteria were kept as broad as possible and the exclusion criteria as restricted as possible to maximize the generalizability of the trial results. Patients were eligible to take part in the trial if they were receiving PD and able to give informed consent. Individuals with a history of psychological illness or any condition which interfered with their ability to understand or comply with the requirements of the study, patients who had an ESI, peritonitis, or tunnel infection within the previous 4 weeks, those who had a known hypersensitivity to, or intolerance of, honey and mupirocin, those who were on long-term antibiotics and those patients with nasal carriage of mupirocin-resistant *Staphylococcus aureus* were excluded from the study.

For the purpose of comparing the characteristics of the trial population with those of the domain population, HONEYPOT trial participants were compared with the Australian and New Zealand PD patient population during the recruitment period with respect to age, gender, ethnicity, body mass index (BMI), smoking status, end-stage kidney disease (ESKD) cause, first renal replacement therapy (RRT) modality, prior history of renal transplantation, first PD modality, history of comorbidities (diabetes mellitus, coronary artery disease, cerebrovascular disease, peripheral vascular disease), prescribed dialysate volume, dialysate small solute clearance, residual renal function (urinary creatinine clearance), dialysate:plasma creatinine ratio at 4 hours, PD solution type, and laboratory parameters (hemoglobin level, serum ferritin concentration, serum calcium concentration, and serum phosphate concentration). All incident and prevalent PD patients on the ANZDATA Registry during the HONEYPOT trial recruitment period were included in the comparison.

STATISTICAL ANALYSIS

Results were expressed as frequencies and percentages for categorical variables, mean ± standard deviation (SD) for continuous normally distributed variables, and median [interquartile range (IQR)] for continuous variables that were not normally distributed. The Chi-squared test was used to compare the 2 groups on categorical variables. Depending on the distributional characteristics of continuous data, the independent-samples *t*-test or Wilcoxon rank-sum test was used to compare the samples. Differences between groups on all characteristics were quantified with standardized difference scores (*d*) where differences of 0.2, 0.5, and 0.8 represent small, medium, and large effect sizes, respectively (25). Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA). *P* values < 0.05 were considered statistically significant.

RESULTS

During the 3-year trial recruitment period, a total of 371 PD patients were recruited into the HONEYPOT trial from 26 centers in Australia and New Zealand. This represented 43% of participants assessed for eligibility in those centers and 6% of all patients receiving PD in Australia and New Zealand at the time (n = 6,085). The baseline characteristics of patients in the HONEYPOT study and those on the ANZDATA Registry are displayed in Table 1.

DEMOGRAPHIC AND CLINICAL DATA

Participants in the HONEYPOT study were approximately 3 years older than patients on the ANZDATA Registry. Compared with patients on the ANZDATA Registry, the HONEYPOT trial participants had lower proportions of Aboriginal and Torres Strait Islander and Maori and Pacific Islander peoples, fewer current smokers, a higher proportion of patients with ESKD due to polycystic kidney disease, and lower proportions of patients with ESKD due to diabetes or glomerulonephritis

TABLE 1
Comparison of Baseline Characteristics for HONEYPOT Trial Participants and Patients on the ANZDATA Registry During the Trial Recruitment Period

	HONEYPOT (*N*=371)	ANZDATA (*N*=6,085)	Standardized difference (HONEYPOT-ANZDATA)*	*P* value
Age (years)				0.003
Mean±SD	61.7±14.5	58.8±16.9	0.19	
Median [IQR]	64 [54,72]	61 [49,72]		
Pediatric				0.123
≤14 years	3 (0.8%)	117 (1.9%)	-0.07	
>14 years	368 (99.2%)	5,968 (98.1%)	0.07	
Gender				0.228
Male	224 (60.4%)	3,480 (57.2%)	0.05	
Female	147 (39.6%)	2,605 (42.8%)	-0.05	
Ethnicity				<0.001
Caucasian	291 (78.9%)	4,074 (67.0%)	0.22	
ATSI	5 (1.4%)	338 (5.6%)	-0.17	
MPI	15 (4.1%)	807 (13.3%)	-0. 25	
Asian	48 (13.0%)	736 (12.1%)	0.02	
Other, *n* (%)	10 (2.7%)	130 (2.1%)	0.03	
Missing	2	0		
Body mass index				0.050
Mean±SD	27.3±5.24	26.9±5.7	0.09	
Median [IQR]	27.0 [23.8,30.6]	26.4 [22.8,30.1]		
Missing	7	42		
Smoking Status				<0.001
Never	151 (40.9%)	2,951 (48.7%)	-0.13	
Former	183 (49.6%)	2,286 (37.7%)	0.20	
Current	35 (9.5%)	827 (13.6%)	-0.10	
Missing	2	21		
Primary cause of end-stage kidney disease				<0.001
Diabetes	87 (23.6%)	2,023 (33.2%)	-0.17	
Hypertension	22 (6.0%)	618 (10.2%)	-0.12	
Glomerulonephritis	65 (17.6%)	1,639 (26.9%)	-0.18	
Analgesic nephropathy	8 (2.2%)	116 (1.9%)	0.02	
Polycystic kidney disease	42 (11.4%)	357 (5.9%)	0.17	
Interstitial nephritis	14 (3.8%)	89 (1.5%)	0.13	
Obstructive nephropathy	3 (0.8%)	97 (1.6%)	-0.06	
Reflux nephropathy	17 (4.6%)	215 (3.5%)	0.05	
Renovascular disease	24 (6.5%)	216 (3.5%)	0.12	
Unknown	24 (6.5%)	347 (5.7%)	0.03	
Other	63 (17.1%)	368 (6.0%)	0.31	
Missing	2	0		
History of renal transplantation prior to starting PD				0.195
No	361 (97.8%)	5,877 (96.6%)	0.06	
Yes	8 (2.2%)	208 (3.4%)	-0.06	
Missing	2	0		
First RRT modality				<0.001
Peritoneal dialysis	269 (72.9%)	3,993 (65.6%)	0.13	
Hemodialysis	92 (24.9%)	2,058 (33.8%)	-0.16	
Transplant	8 (2.2%)	34 (0.6%)	0.13	
Missing	2	0		
First PD modality				<0.001
APD	191 (51.8%)	1,254 (20.6%)	0.58	
CAPD	178 (48.2%)	4,831 (79.4%)	-0.58	
Missing	2	0		

TABLE 1 (cont'd)

	HONEYPOT (*N*=371)	ANZDATA (*N*=6,085)	Standardized difference (HONEYPOT-ANZDATA)*	*P* value
Diabetes mellitus				<0.001
No	254 (68.8%)	3,528 (58.0%)	0.18	
Yes	115 (31.2%)	2,557 (42.0%)	-0.18	
Missing	2	0		
Coronary artery disease				<0.001
No	259 (70.2%)	3,726 (61.2%)	0.15	
Yes	110 (29.8%)	2,359 (38.8%)	-0.15	
Missing	2	0		
Cerebrovascular disease				0.139
No	325 (88.1%)	5,189 (85.3%)	0.07	
Yes	44 (11.9%)	896 (14.7%)	-0.07	
Missing	2	0		
Peripheral vascular disease				<0.001
No	317 (85.9%)	4,637 (76.2%)	0.20	
Yes	52 (14.1%)	1,448 (23.8%)	-0.20	
Missing	2	0		
Total volume of weekly exchanges				0.02
Mean±SD	9.1±3.0	9.6±2.9	-0.16	
Median [IQR]	8.2 [8.0,10.0]	8.6 [8.0,11.0]		
Missing	2	302		
Dialysate creatinine clearance				<0.001
Mean±SD	42.0±15.6	46.1±22.7	-0.21	
Median [IQR]	40.0 [33.0,48.0]	42.9 [35.5,52.0]		
Missing	49	1,979		
Dialysate weekly Kt/V				0.037
Mean±SD	1.6±0.6	1.7±0.6	-0.09	
Median [IQR]	1.5 [1.2,1.9]	1.6 [1.3,2.0]		
Missing	43	1,977		
Residual renal function (L/week/1.73 m^2)				<0.001
Mean±SD	49.6±39.4	39.1±41.1	0.26	
Median [IQR]	45.0 [18.0,74.0]	29.9 [7.0,58.7]		
Missing	55	1,981		
D:P creatinine at 4 hours				0.750
Mean±SD	0.68±0.14	0.68±0.10	0.02	
Median [IQR]	0.68 [0.61,0.76]	0.69 [0.60,0.77]		
Missing	67	2,170		
PD solution				0.929
Neutral pH low GDP	22 (6.0%)	338 (5.8%)	0.004	
Other	347 (94.0%)	5,440 (94.2%)	-0.004	
Missing	2	307		
Hemoglobin (g/L)				0.088
Mean±SD	114.2±16.1	113.2±16.1	0.06	
Median [IQR]	115 [105,123]	113 [103,123]		
Missing	4	54		
Serum ferritin (ng/mL)				<0.001
Mean±SD	310.6±270.9	391.8±433.2	-0.22	
Median [IQR]	241 [102,420]	278 [137,502]		
Missing	38	574		
Calcium (mmol/L)				<0.001
Mean±SD	2.29±0.19	2.25±0.22	0.20	
Median [IQR]	2.3 [2.2,2.4]	2.3 [2.1,2.4]		
Missing	8	59		
Phosphate (mmol/L)				0.021
Mean±SD	1.62±0.47	1.68±0.52	-0.13	

TABLE 1 (cont'd)

	HONEYPOT (*N*=371)	ANZDATA (*N*=6,085)	Standardized difference (HONEYPOT-ANZDATA)*	*P* value
Phosphate (mmol/L) (cont'd)				
Median [IQR]	1.60 [1.30,1.80]	1.61 [1.32,1.97]		
Missing	12	58		

ANZDATA = Australia and New Zealand Dialysis and Transplant; SD = standard deviation; IQR = interquartile range; ATSI = Aboriginal and Torres Strait Islander; MPI = Maori and Pacific Islander; PD = peritoneal dialysis; RRT = renal replacement therapy; APD = automated PD; CAPD = continuous ambulatory PD; D:P Creatinine = dialysate/plasma creatinine; GDP = glucose degradation product.
* Standardized difference = difference in means or proportions divided by standard error.

(Table 1). HONEYPOT trial participants were also significantly less likely to have been treated with hemodialysis prior to PD, more likely to have been treated with automated PD (APD), and less likely to have diabetes mellitus, coronary artery disease and peripheral vascular disease (Table 1). No differences were observed between HONEYPOT trial participants and patients on the ANZDATA Registry with respect to gender, body size, or history of prior renal transplantation.

PARAMETERS OF PERITONEAL DIALYSIS

The median residual renal function of participants in the HONEYPOT study (45 L/week/1.73 m^2) was appreciably higher than in patients on the ANZDATA Registry (29.9 L/week/1.73 m^2) ($p < 0.001$). The prescribed volume of weekly exchanges and dialysate creatinine clearance values were lower in the HONEYPOT group than in patients on the ANZDATA Registry (Table 1). Prescription of neutral pH, low glucose degradation product (GDP) fluids was comparable between the HONEYPOT participants and ANZDATA Registry patients (Table 1).

BIOCHEMICAL RESULTS

Hemoglobin levels were comparable between the trial and registry groups (Table 1). Serum ferritin concentration was significantly lower in the HONEYPOT participants than in the patients on the ANZDATA Registry (median 241 vs 278 ng/mL, $p < 0.001$). Serum calcium concentration was marginally higher by an average value of 0.04 mmol/L in the HONEYPOT cohort compared with the ANZDATA patients (Table 1). Serum phosphate concentration was also marginally lower in the HONEYPOT patients compared with those on the ANZDATA Registry (mean 1.62 vs 1.68 mmol/L, $p = 0.02$).

DISCUSSION

One of the most frequent criticisms of RCTs by clinicians is lack of consideration of the applicability of the study's findings to the routine clinical setting (15). Often the major concern affecting the applicability of RCTs is ascertainment bias, whereby patients recruited into the trial represent only a small proportion of the domain population and are not truly representative of that broader patient population. Moreover, RCTs often exclude important patient groups, such as women (26), the elderly (26,27) and patients at risk of treatment complications (15).

In this retrospective, cross-sectional observational study, the baseline characteristics of the HONEYPOT trial participants were compared with PD patients on the ANZDATA Registry during the trial recruitment period. The results indicated that HONEYPOT trial participants differed from the population of Australian and New Zealand PD patients in a number of important respects. Specifically, the HONEYPOT study group was older, had better residual renal function, had higher proportions of participants with ESKD due to polycystic kidney disease and who were treated with APD, and had lower proportions of indigenous people, current smokers, and patients with a prior history of hemodialysis, diabetes mellitus, coronary artery disease or peripheral vascular disease. HONEYPOT trial participants also had lower serum ferritin and phosphate levels and higher serum calcium levels.

Consequently, despite having very broad inclusion criteria and very few exclusion criteria to ensure that a high proportion of PD patients were eligible for the HONEYPOT trial, it would appear that some further selection of trial participants occurred beyond the eligibility criteria to result in a population with characteristics that differed from the general PD patient population. According to HONEYPOT trial screening logs, only 11% of the 872 participants assessed for eligibility for the HONEYPOT trial did not meet inclusion criteria, whilst 32% were excluded due to patient refusal and 15% were excluded due to other reasons such as physician refusal. These results are in keeping with the findings of a previously published survey of 41 United States National Institute of Health RCTs in which losses of eligible subjects prior to randomization were attributable to refusals by patients in 25% and refusals by physicians in 29% (28). Whilst very few trials documented the characteristics of patients who were eligible but not entered, these patients differed clinically from those enrolled.

Although many of the differences between the HONEYPOT participants and the Australian and New Zealand PD patient population were clinically modest, it is possible that the cumulative effect of these differences may have been relevant

to the primary outcome of the study (PD-related infections). For example, overall peritonitis risk in the HONEYPOT patient population may have been on the one hand increased by their older age (18,22) and on the other hand lowered by their higher residual renal function (21) and lower proportions of indigenous patients (2,18–20), current smokers (2), and patients with prior histories of hemodialysis treatment (29), diabetes mellitus (2,18), and cardiovascular disease (18,20). These factors may have contributed to the lower observed overall peritonitis rate in the HONEYPOT study (0.35 episodes per patient-year) (12) compared with the peritonitis rates reported by the ANZDATA Registry during the same period (0.62, 0.58, 0.53, and 0.43 episodes per patient-year for 2008, 2009, 2010, and 2011, respectively) (30). The lower observed peritonitis rates in the HONEYPOT trial may also be attributable in part to a Hawthorne effect whereby trial participants and physicians adopted improved PD practices by virtue of their awareness of being observed in a trial.

Given that the differences in characteristics between the HONEYPOT trial participants and the Australian and New Zealand PD patient populations may have led to different peritonitis risks and rates, it is also possible that these differences in characteristics modified the effects of the intervention on the outcome. In pre-specified sub-group analyses of the HONEYPOT study, the effect of honey on PD-related infections was not modified by age, body size, PD modality, nasal staphylococcal carriage or whether the participant was a prevalent or incident patient (12). However, honey was observed to be inferior to mupirocin in subjects with diabetes mellitus. Of the remaining patient characteristics that differed between the HONEYPOT and ANZDATA cohorts, the most potentially significant was ethnicity, whereby HONEYPOT participants were much less likely to be Aboriginal and Torres Strait Islander (1.4% vs 5.6%, respectively) or Maori and Pacific Islander (4.1% vs 13.3%). However, the numbers of these patients in the HONEYPOT trial (5 and 15, respectively) were too small to permit meaningful analysis of possible effect modification. Therefore, the applicability of the findings of the HONEYPOT trial to these populations remains uncertain. To allow an assessment of the effects of honey in this important subgroup, Aboriginal and Torres Strait Islander or Maori and Pacific Islander could be oversampled in future RCT designs.

The study had a number of limitations, mainly that the comparatively limited data collected by the ANZDATA Registry restricted comparison of the characteristics of the HONEYPOT and ANZDATA populations. ANZDATA does not collect important information that may have helped to better determine the representativeness of the HONEYPOT trial group, such as PD prescription, education level, literacy, patient compliance, cognitive function, mental health conditions, socio-economic status, individual unit management protocols (including infection control policies and procedures), ESI and tunnel infections. The contribution of center effects to differences between the HONEYPOT and ANZDATA cohorts could not be evaluated. Nevertheless, the HONEYPOT trial did involve approximately 40% of all Australian and New Zealand PD units and included a mix of centers (metropolitan vs regional, teaching vs non-teaching) that were widely geographically distributed throughout both countries. As comparisons were only made against Australian and New Zealand PD patients, the generalizability of the HONEYPOT trial to other countries and healthcare systems is uncertain.

In conclusion, despite the broad inclusion criteria of the HONEYPOT study, the baseline characteristics of trial participants differed in a number of aspects from the Australian and New Zealand PD patient population. Although the differences between the groups were generally modest, it is possible that their cumulative effect may have had some impact on external generalizability, which is not an uncommon occurrence in clinical trials. The relatively small numbers of Aboriginal and Torres Strait Islander and Maori and Pacific Islander peoples mean that the applicability of the findings of the HONEYPOT trial to these populations remains uncertain.

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DISCLOSURES

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