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The Role of Clinical Pharmacist in Reducing Drug Related Problems in Hemodialysis Patients

Aya F. Talib[*,1] and Zinah M.Anwer [**]

[*] Ministry of Health and Environment Al-Karkh Health Directorate, , Baghdad, Iraq

[**]Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq

Abstract

Prescribing drugs to patients to treat ailments or reducing their morbidity may not be enough, even if the drugs were all indicated and in the right dose. Clinical pharmacists play a pivotal role in conducting information and instruction to patients and conveying feedback to treating physician when appropriate, and the final goal is in the interest of the patient. The aim of the study was detection and classification of any drug related problems among hemodialysis patients and trying to reduce them by providing suitable recommendations in collaboration with the health care providers. Prospective, interventional, clinical study for 180 hemodialysis patients, and was designed as two phases, an observational phase to identify drug related problems and classifying them according to the latest Pharmaceutical Care Network Europe classification, and an interventional phase to increase the awareness of patients and the nephrologists about those problems and proposing a proper solution for each one. The main drug related problems was related to the effect of drug treatment being not optimal in 58.7%, followed by no effect in 17.8%, and least for unrelated symptoms or indications in 4.8%; causes were inappropriate combination and patients taking less drug than prescribed (both 17.4%), followed by no/or incomplete drug treatment in spite of existing indication in 12.2%, drug without indication in 10.4%. Erythropoietin and calcium were the most frequently drugs with problems. Acceptance and full implementation were observed in 34.3% of recommendations, while about half of the drug related problems had unknown implementation (51.3%). There were significant numbers of drug related problems among Iraqi patients on hemodialysis, the use of erythropoietin, calcium carbonate and sevelamer was responsible for most of inappropriate combinations. Physicians and clinical pharmacist cooperation was excellent.

Keywords: Drug related problems, Hemodialysis, Clinical pharmacist. Pharmaceutical care, Iraq.

دور الصيدلي السريري في تقليل المشاكل العلاجية لمرضى الغسل الكلوي

اية فوزي طالب[*،1] و زينة مظفر انور [**]

[*] وزارة الصحة والبيئة ، دائرة صحة بغداد، الكرخ .

[**] فرع الصيدلة السريرية، كلية الصيدلة، جامعة بغداد ، بغداد ، العراق .

الخلاصة

وصف الأدوية للمرضى لعلاج أمراضهم أو الحد من اعراض المرض قد لا يكون كافياً، حتى لو تم تحديد جميع الأدوية بصورة صحيحة وبالجرعة المناسبة. يلعب الصيادلة السريريون دورًا محوريًا كحلقة وصل لنقل المعلومات والتعليمات للمرضى وايصال التغذية الارجاعية إلى الطبيب المعالج عند الحاجة لذلك، فالهدف النهائي هو مصلحة المريض.

تحديد وتصنيف المشاكل المتعلقة بالادوية ومناقشتها مع الاطباء الذين يقدمون الرعاية الصحية.

دراسة تقدمية، تداخلية وسريرية لـ ١٨٠ مريضاً يخضعون لغسيل كلوي، وتم تصميمها على مرحلتين، مرحلة مراقبة لتحديد المشاكل المتعلقة بالادوية وتصنيفها وفقًا لأحدث تصنيف لشبكة الرعاية الصيدلانية في أوروبا ، و تبعتها مرحلة تداخلية لزيادة وعي المرضى وأطباء أمراض الكلى حول تلك المشاكل واقتراح حل مناسب لكل منها.المشاكل الرئيسية المتعلقة بالادوية ارتبطت بتأثير العلاج الدوائي الذي لم يكن مثالياً في ٥٨,٧٪، يليه عدم فعالية الدواء في ١٧,٨٪، ثم ٤,٨٪ لعدم ترابط الادوية مع الاعراض او اسباب استخدامها. اشتملت اسباب المشاكل المتعلقة بالادوية على تزامن استخدام ادوية لا تتناسب مع بعضها، وتناول جرعة الادوية أقل من الموصوف (١٧,٤ ٪) من قبل الطبيب، متبوعًا بعدم استخدام علاج معين على الرغم من وجود مؤشرات لذلك في ١٢,٢ ٪ ، واستخدام دواء معين بدون مؤشر لذلك في ١٠,٤ ٪. كان الإريثروبويتين والكالسيوم أكثر الأدوية التي عانت من مشاكل في استخدامها. ولوحظ تقبل الاطباء واجراء كل التوصيات في ٣٤,٣٪ حالة، بينما نصف توصيات لحل المشاكل المتعلقة بالادوية لم يكن يعرف تطبيقها من عدمه (٥١,٣٪).

كان هناك عدد كبير من المشاكل المتعلقة بالادوية بين المرضى العراقيين تحت غسيل الكلى، وكان استعمال دواء الارثروبويتين والكالسيوم والسفيلامير الاكثر مسؤولية عن التسبب بالتداخلات الدوائية. كان التعاون بين الأطباء والصيادلة السريريين ممتازًا.

الكلمات المفتاحية: المشاكل المتعلقة بالادوية، الغسل الكلوي، الصيدلي السريري،الرعاية الصيدلانية،العراق .

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[1]Corresponding author E-mail**:** ayaftalib@google.com

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Introduction

Worldwide Chronic Kidney Disease (CKD) is one of the most common noncommunicable diseases, and in 2015 it was the twelfth cause of death, responsible for 1.1 million deaths [(1)]. End-stage renal disease (ESRD) is defined as irreversible decline in a person's own kidney function, which is severe enough to be fatal in the absence of dialysis or transplantation [(2)].

The ESRD can present with a number of signs and symptoms. Some include volume overload not responding to diuretics, hypertension with low response to therapy, anemia, and metabolic derangements like hyperkalemia, hyponatremia, metabolic acidosis, hypo/hypercalcemia, and hyperphosphatemia. Uremic toxicity can present as loss of appetite, nausea, vomiting, bleeding tendency, neuropathy or encephalopathy, seizures, loss of consciousness, with high mortality rate and it's an urgent indications dialysis [(3)]. Generally, the symptoms of ESRD appear in stages 4 and 5 when the glomerulus filtration rate (GFR) falls below 30 ml/min, but sometimes the underlying etiology presents earlier like in cases of nephrotic syndrome and cystic renal diseases [(4)].

Drug-Related Problems (DRPs) are events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes [(5)]. Pharmaceutical Care Network Europe (PCNE) had developed a classification scheme DRPs in 1999 and still continuously updated, the most recent version (9.0) last updated June 2019 and included: problems, causes and interventions [(6)]. The evidence of the benefits of the pharmacists' interventions in patients with CKD is sparse, with variable quality and unharmonious outcomes, however, on the basis of best available evidence it may have a positive impact on outcomes of patients with CKD [(7)]. The major DRPs in patients on hemodialysis may include drug interactions, adverse reactions [(8)], under dose and treatment failure [(9)].

Aim of the study was detection and classification of any drug related problems among hemodialysis patients and trying to reduce them by providing suitable recommendations in collaboration with the health care providers.

Patients and methods

Study design

This prospective, interventional, clinical study was designed as two phases, an observational phase to determine the prevalence of DRPs, identifying and classifying them using the latest version of PCNE [(6)] and an interventional phase in which the researcher pharmacist increased the awareness of patients and the nephrologists about DRPs and proposed a proper solution for each type of DRPs .

This study was carried out in two hemodialysis centers one in Baghdad Teaching Hospital in the Medical City Complex and the second in Al-Imamain Al-Kathymain Medical City. Data was collected from the first of December 2019, until the 29th of February 2020.

The sample size was calculated by a single population proportion formula with a 95% level of confidence and after adjusting the data for the finite sample size of 400 that were registered; the final sample size was 175 and a total of 180 patients were enrolled in the study.[(10, 11)]

Inclusion criteria

1. Outpatients aged ≥20 years with end stage renal disease on regular hemodialysis session.
2. Agree to participate in the study
3. Are registered patients for hemodialysis.

Exclusion criterion

1. Patients infected with Hepatitis B or C.
2. Pregnant or breast-feeding women.
3. Patients admitted for investigational purposes without hemodialysis.

Data collection/ Observational phase

A special sheet was designed by the research team to match study goals and the information was collected from patients' case-sheets regarding their demographic data, comorbidities, laboratory investigations, medication history, Hemodialysis sessions number and related drugs and by participating in daily morning tours with the physicians and the clinical pharmacist. All information was double checked with the patients themselves, caregivers, or physicians.

The researcher was concerned with identifying any type of DRPs, then classifying it according to PCNE classification scheme [(6)].

Data collection/ Interventional phase

This interventional phase was done concomitantly with the observational phase and included offering proper clinical-pharmacological interventions, both on patients' level, and physicians' level, which was based on Kidney Disease Improving Global Outcomes (KDIGO) Guidelines [(12)] then assessing the acceptance of the physicians to this intervention.

Patients level

Included 2 types according to PCNE:

1. Offering a proper patient counseling.
2. Written information was provided to the patient.

Physicians' level

Proposing a proper clinical intervention according to KDIGO Guidelines [12] after interpretation of patient's lab data, clinical status and comorbidities.

All the prescribed medications were checked for interactions and identified using the Medscape and given the code C1.4 from PCNE. Direct interviewing, then assessing the acceptance and implementation of the physicians to this intervention. Those interventions for the physicians were accompanied with information from the references in order to persuade the physicians to make the required change suggested by the researcher.

Ethical considerations

A research proposal was approved by the Scientific Committee of the College of Pharmacy/ University of Baghdad before it was submitted and officially approved. Additionally, the study was approved by the hospitals, and participants' verbal consent was obtained.

Statistical analysis

All the categorical data were expressed in the form of frequency numbers and percentages while the continuous data were summarized as means and standard deviations. Various comparison tests were conducted for different variables between the patients and a p-value less than 0.05 was considered significant. Chi-square was used for the categorical data comparisons and replaced with Fisher's exact test in case the first was inapplicable. Also, independent sample t-test for binary comparisons. All the statistical work and the graphs were done using the Statistical Package for the Social Sciences (SPSS) software version 22.

Results

The most frequent age group was 60-69 years, about half of the study sample was male(52%), and 39.4% of the study group were overweight, 23.3% class I obese and only 2.8% class II obese, as shown in Table (1).

Table 1.Basic demographic data of the study sample

Variable	Number	%
Age groups		
20-29	14	7.8
30-39	10	5.6
40-49	23	12.8
50-59	41	22.8
60-69	63	35.0
≥70	29	16.1
Gender		
Male	94	52.2
Female	86	47.8
BMI		
Underweight	8	4.4
Normal weight	54	30.0
Overweight	71	39.4
Class I obesity	42	23.3
Class II obesity	5	2.8
Total	180	100.0

The main DRPs was related to the effect of drug treatment being not optimal, in 58.7%, followed by no effect in 17.8%, and least for unrelated symptoms or indications in 4.8%, as shown in Table (2).

Table 2. Distribution of the study sample according to main DRPs.

Main DRPs	Number	%
No effect of drug treatment	41	17.8
Effect of drug treatment not optimal	135	58.7
Untreated symptoms or indication	11	4.8
Adverse drug event (possibly) occurring	21	9.1
Unnecessary drug-treatment	22	9.6
Total	230	100.0
DRPs: drug related problems.		

There were 21 cases (9.1%) with adverse events, which did not need further explanation for causes of DRP according to the PCNE. The most frequent causes were inappropriate combination and patients taking less drug than prescribed (both 17.4%), then followed by no/or incomplete drug treatment in spite of existing indication in 12.2%, then no indication for the drug in 10.4%, the details are shown in Table 3.

Table 3. Distribution of the study sample according to causes of DRP

Causes of DRP	Number	%
Adverse drug event (possibly) occurring	21	9.1
Inappropriate drug according to guidelines/formulary	7	3.0
No indication for drug	24	10.4
Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	40	17.4
Inappropriate duplication of therapeutic group or active ingredient	1	0.4
No or incomplete drug treatment in spite of existing indication	28	12.2
Drug dose too low	22	9.6
Drug dose too high	12	5.2
Duration of treatment too short	5	2.2
Duration of treatment too long	1	0.4
Prescribed drug not available	1	0.4
Inappropriate timing of administration or dosing intervals	1	0.4
Patient uses/takes less drug than prescribed or does not take the drug at all	40	17.4
Patient uses/takes more drug than prescribed	6	2.6
Inappropriate timing or dosing intervals	21	9.1
Total	230	100.0

Erythropoietin was the most frequently encountered, with the patients taking less than prescribed dose. Followed by calcium DRPs, which were commonly inappropriate dosing/ timing or interactions. Sevelamer was usually used inappropriately combined with folic acid. Ferrous sulfate DRPs were caused commonly dose related. Cinacalcet DRPs mainly caused adverse reactions. Amlodipine DRPs mainly were patient related. Omeprazole, anti-histamines and antipyretic all were not or incompletely used as shown in Table (4).

Table 4. Distribution of medications according to cause of DRP expressed as number(percentage).

Drugs	Erythropoietin	Calcium	Sevelamer	Ferrous sulfate	Cinacalcet	Amlodipine	Omeprazole	Anti-histamine	Antipyretic	Total
Adverse reactions	1(4.8)	7(33.3)	1(4.8)	1(4.8)	11(52.4)	0(0)	0(0)	0(0)	0(0)	21(100)
Inappropriate drug	0(0)	2(28.6)	5(71.4)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	7(100)
No indication for drug	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)
Inappropriate combination of drugs	0(0)	12(38.7)	18(58.1)	0(0)	1(3.2)	0(0)	0(0)	0(0)	0(0)	31(100)
No or incomplete drug treatment	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	5(41.7)	4(33.3)	3(25)	12(100)
Drug dose too low	7(38.9)	0(0)	3(16.7)	8(44.4)	0(0)	0(0)	0(0)	0(0)	0(0)	18(100)
Drug dose too high	4(33.3)	0(0)	4(33.3)	4(33.3)	0(0)	0(0)	0(0)	0(0)	0(0)	12(100)
Patient uses/takes less drug than prescribed or does not take the drug at all	35(87.5)	0(0)	1(2.5)	2(5)	0(0)	2(5)	0(0)	0(0)	0(0)	40(100)
Patient uses/takes more drug than prescribed	0(0)	0(0)	0(0)	0(0)	0(0)	5(100)	0(0)	0(0)	0(0)	5(100)
Inappropriate timing or dosing intervals	1(4.8)	17(81)	1(4.8)	0(0)	2(9.5)	0(0)	0(0)	0(0)	0(0)	21(100)
	48(28.6)	38(22.6)	34(20.2)	15(8.9)	14(8.3)	7(4.2)	5(3)	4(2.4)	3(1.8)	168(100)

Acceptance and full implementation were observed in 34.3%, while about half of the DRPs had unknown implementation (51.3%), and no agreement occurred with 7.8% of the cases, as shown in Table (5).

Table 5. Distribution of the study sample according to acceptance per planned intervention

Acceptance	Number	%
Intervention accepted and fully implemented	79	34.3
Intervention accepted, partially implemented	10	4.3
Intervention accepted but not implemented	5	2.2
Intervention accepted, implementation unknown	118	51.3
Intervention not accepted: no agreement	18	7.8
Total	230	100.0

Discussion

Drug related problems are common medical/ pharmaceutical outcomes, especially in patients with end stage renal disease requiring replacement therapy like hemodialysis; with increasing number of drugs and complicated medication regimens, with multiple medical conditions that might require polypharmacy, however, not all the problems is due to prescriptions errors, some are unpredictable complications, or potential errors that could be prevented with modifications of some behaviors [(9)].

In the current study, the main DRPs was suboptimal drug effect followed by no effect and least for unrelated symptoms or indications. In Solaimani/ Iraq, Ossman and colleagues (2015) studied DRP in 50 CKD patients on hemodialysis, but they did not use PCNE classification, and reported that commonest DRPs were under dose in 29%, treatment failure in 27.7% and 14.7% for incorrect administration [(9)]. In another study done in Saudi Arabia by Alshamrani et al., (2018), that studied polypharmacy and DRPs in 83 patients on hemodialysis and reported that 36% of DRPs were related to using drug without indication, 23% sub-therapeutic doses, 15% overdosing and 10% not using indicated drugs [(13)]. These findings were in partial concordance to the results of Ramadaniati et al., (2016) in Indonesia, who enrolled 105 patients and reported that there were 1026 actual and potential DRPs during their study period, 38.9% were non allergic adverse effects, 28.7% were suboptimal effect, and 9.8% were no effect of drug [(14)]. It can be seen that in all the previously mentioned studies, the DRPs were different, this could reflect the complexity of CKD and hemodialysis who usually requires multiple medications and complications of CKD and the associated co-morbidities, and with that the burdens increase on the patients and the treating physicians, here comes the role of the clinical pharmacist in elaborating, facilitating, and actively taking role in arrangement of the drugs and guiding the treating physician towards safer treatment options.

In the current study, the most frequent causes of DRPs were inappropriate combination and patients taking less drug than prescribed, followed by no/or incomplete drug treatment in spite of existing indication, then using drugs without indication. These findings were comparable to results of a study done by Nijeri (2016) in Kenya, who enroled 60 hemodialysis patients in his thesis, and he observed 271 DRPs, from which 21.8% were drug interactions, 18.1% not using indicated drugs, 9.2% using drugs without indications, and 7% dose is too low [(15)]. Patricia and Foote (2016) in Unites States, who enrolled 93 hemodialysis patients with 376 medical discrepancies and 66 DRPs, they reported that 37.5% of DRPs were not using an indicated drug, 20.3% higher than recommended dose, 18.8% using drugs without indication, and 7.8% for drug-drug interactions [(16)]. While in India, George et al., (2017) who enrolled 79 patients undergoing hemodialysis and reported that the vast majority of DRPs (86.4%) were drug interaction (260 out of 301 DRPs), from them 13.07% were serious and 75% were moderate but significant and 11.92% were mild, and the other DRPs were adverse drug reactions (4.98%) [(8)]. It can be seen that drug interactions are common among patients with CKD and this can be explained as those patients usually need calcium carbonate supplementations, and it has a considerable list of interactions, including some antibiotics (tetracyclines and quinolones), bisphosphonates (which might also be needed for some patients), calcium channel blockers, iron supplements (ferrous sulfate) and low dose of aspirin. The other cause could be polypharmacy associated with those patients (8.35 ± 2.33 drugs per prescription as reported by George el al., [(8)]), which complicates the situation even with the aid of the clinical pharmacist.

Regarding certain DRPs in the current study, the findings were comparable to results of Ossman et al., (2015) who reported that iron supplements and erythropoietin had the highest DRPs which were related to treatment failure and under-dosing, followed by calcium carbonate which were related to incorrect administration and non-adherence by patients, then antihypertensive drugs related to treatment failure, other drugs included anti-histamines, sevelamer and alfacalcidol [(9)]. Lumbantobing et al., (2017) in Indonesia, studied 86 patients on hemodialysis and reported a total of 337 DRPs, and the drugs that commonly cause these problems were calcium carbonate (52.23%), ferrous sulfate (18.69%), erythropoitin (9.5%) and

omeprazol (9.5%) [17]. From this information, it can be deducted that calcium supplements causes a lot of DRPs, one cause could be the large number of patients with CKD who requires calcium because of increased serum phosphorus and decreased renal production of 1,25 $(OH)_2$ vitamin D. Ferrous sulfate also is needed in large number of patients due to low or absent production of erythropoietin and the anemia of chronic disease.

The interventions in the current study were accepted in 92.2% of DRPs and were fully implemented in 34.3%, however, 51.3% the implementations were unknown. Lower acceptance rates were reported by Patricia and Foote (2016) in Unites States, as 77% of the interventions made by the clinical pharmacist were accepted, but they mentioned that some interventions were less readily accepted, which included dosage of drugs, not using an indicated drug, and using an unindicated drug [16]. In another recent study done by Savitha et al., (2020) in India, who enrolled 833 patients and identified 250 DRPs, and reported a very high acceptance and implementation of 97.6% [18]. The high percent of unknown implementation was due to difficulties in following the patients after advising them about the DRPs and whether they actually adhered to the given recommendations. Clinical interventions were introduced to help improving patients' outcome, through actively participating in identifying DRPs, and offering proper clinical interventions to the treating physician or the nurse in some situations, or directly to patients, for example improving their adherence to therapy. The corporation between the medical and pharmaceutical branches definitely yield better results.

Limitations

The most important limitations that were encountered are the Unavailable laboratory investigations in the hospitals which were necessary for calculating the required doses, like parathyroid hormone levels and iron study, also Most patient were tired and have low motivation for sharing information, in addition nor relatives were allowed to enter the hemodialysis centers and last the schedule of hemodialysis session starts as early as 4 am in the morning, so it was not feasible to obtain information from all patients when.

Conclusions

1. There were significant numbers of DRPs among Iraqi patients on hemodialysis, and the commonest one was suboptimal effect of drug.
2. The main causes of the DRPs were inappropriate combinations and patients not taking the recommended doses, and the main drugs responsible were erythropoietin, calcium carbonate and sevelamer.
3. Physicians and clinical pharmacist cooperation were excellent, and high percent of unknown implementation was related to patients' factors.

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