JMPF Vol. 10 No. 3 : 167-175
ISSN-p : 2088-8139
ISSN-e : 2443-2946

Evaluasi Kualitas Hidup Pasien Kanker Serviks yang Mendapat Regimen Kemoterapi Cisplatin-Vinkristin-Bleomisin dan Carboplatin-Paklitaksel

Quality of Life Evaluation of Cervical Cancer Patients with Delivered Cisplatin-Vincristine-Bleomycin and Carboplatin-Paclitaxel Chemotherapy Regimens

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Submitted: 25-03-2019 *Revised: 29-05-2019* *Accepted: 11-09-2020*
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ABSTRAK

Kanker serviks merupakan salah satu jenis kanker dengan prevalensi tinggi pada wanita. Kualitas hidup seseorang akan menurun jika menderita kanker serviks. Pada penderita, penurunan kualitas hidup tidak hanya karena faktor penyakit kanker serviks, namun, regimen kemoterapi juga akan mempengaruhi. Tujuan penelitian ini adalah untuk mengevaluasi dampak penggunaan regimen cisplatin-vinkristin-bleomisin dan carboplatin-paklitaksel terhadap kualitas hidup pasien. Melalui penelitian ini dapat diketahui bagaimana perbedaan kualitas hidup pasien kanker serviks pada sebelum dan setelah kemoterapi. Selain itu diamati pula apakah terdapat perbedaan dalam dampaknya terhadap kualitas hidup dari kedua regimen tersebut. Penelitian dilakukan menggunakan rancangan *cross sectional* pada pasien rawat inap. Data diambil secara prospektif dengan observasi lapangan. Pengukuran kualitas hidup dilakukan menggunakan kuesioner EORTC QLQ-C30. Perbedaan nilai domain sebelum dan setelah kemoterapi pada tiap regimen dianalisis dengan *paired t-test* ($p<0,05$). Perbedaan kualitas hidup dari kedua regimen dianalisis dengan *unpaired t-test* ($p<0,05$). Hasil menunjukkan terdapat kecenderungan peningkatan nilai domain fungsional, penurunan nilai domain gejala dan peningkatan nilai domain status kesehatan global setelah kemoterapi tiga siklus pada kedua regimen, kecuali gejala mual dan muntah serta kehilangan nafsu makan yang menunjukkan kecenderungan peningkatan. Pasien yang mendapatkan regimen cisplatin-vinkristin-bleomisin menunjukkan peningkatan yang bermakna ($p=0,009$) pada gejala penurunan nafsu makan. Tidak terdapat perbedaan bermakna pada kualitas hidup pasien yang mendapatkan kemoterapi regimen cisplatin-vinkristin-bleomisin dibandingkan terhadap regimen carboplatin-paklitaksel.
Kata kunci: kanker serviks; kemoterapi; kualitas hidup; EORTC QLQ-C30

ABSTRACT

Cervical cancer is one type of cancer with a high prevalence in women. Quality of life of someone with cervical cancer will decrease. Quality of life can also decrease because of chemotherapy regimens. The purpose of this study was to evaluate the impact of cisplatin-vincristine-bleomycin and carboplatin-paclitaxel regimens on the quality of life of patients. Through this research, how the difference in quality of life of patients with cervical cancer before and after chemotherapy could be known. Additionally, the differences impact on the quality of life of the two regimens also were observed. The study was conducted by using cross sectional design in hospitalization patients. Data were taken prospectively by conducting field observations. Measuring the quality of life was done using the EORTC QLQ-C30 questionnaire. Differences of domain values before and after chemotherapy in each regimen were analyzed by paired t-test ($p <0.05$). Quality of life difference between two regimens were analyzed by unpaired t test ($p<0.05$). The results showed that there was an increasing trend of the value of the functional domain, impairment of symptoms domain and an increase in the value of global health status domain after three cycles of chemotherapy of two regimens, except the symptoms of nausea and vomiting and loss of appetite that showed an increasing trend. Patients who received cisplatin-vincristine-bleomycin regimen showed a significant increasing ($p = 0.009$) in decreased of appetite symptom's scores. No significant differences in the quality of life of patients who delivered chemotherapy regimen of cisplatin-vincristine-bleomycin compared to carboplatin-paclitaxel regimen.

Keywords: cervical cancer; chemotherapy; quality of life; EORTC QLQ-C30

PENDAHULUAN

Kanker serviks adalah kanker nomor dua yang paling umum pada wanita di seluruh dunia. Diperkirakan 500.000 wanita didiagnosis menderita kanker serviks tiap tahun. Selain itu diperkirakan lebih dari 50% penderita meninggal karena penyakit ini[1].

Kualitas hidup seseorang akan menurun jika menderita kanker. Penurunan kualitas hidup pada penderita juga disebabkan oleh kemoterapi. Kemoterapi dapat mengakibatkan perubahan pada status fungsional pasien akibat efek samping yang ditimbulkan. Berdasarkan hasil penelitiaan di RSUP Dr. Sardjito, Yogyakarta, terjadi penurunan kualitas hidup pada pasien berupa peningkatan gejala muntah selama menggunakan cisplatin sebagai monoterapi atau sebagai kombinasi dibandingkan sebelum menjalani kemoterapi[2]. Penelitian di Yunani menunjukkan hasil yang berbeda. Hasil menunjukkan bahwa kemoterapi yang diberikan sebagai bagian dari kemoradiasi tidak berdampak bermakna terhadap kualitas hidup pasien[3].

Cisplatin-vinkristin-bleomisin (PVB) merupakan regimen yang direkomendasikan oleh Kementrian Kesehatan[4]. Regimen carboplatin-paklitaksel direkomendasikan sebagai terapi kombinasi lini pertama menurut NCCN[5]. Meskipun kedua regimen tersebut diketahui merupakan regimen yang direkomendasikan oleh beberapa panduan pengobatan kanker, namun dampaknya terhadap kualitas hidup pasien perlu dievaluasi.

Penelitian yang telah dilakukan mengenai dampak terhadap kualitas hidup adalah regimen carboplatin-paklitaksel. Pemberian regimen tersebut pada 12 pasien di Rumah Sakit Sanglah, Denpasar, meningkatkan kualitas hidup pasien secara bermakna[6]. Selain itu telah dilakukan pula penelitian mengenai kualitas hidup pasien kanker dengan regimen yang terdiri dari bleomisin dan kemoterapi berbasis platinum yaitu bleomisin-oncovin-mitosin-platinum (BOMP) juga di RS Sanglah. Berdasarkan penelitian tersebut regimen BOMP terbukti memperbaiki kualitas hidup pasien[7].

Kombinasi cisplatin-vinkristin-bleomisin dan kombinasi carboplatin-paklitaksel merupakan dua regimen yang sering digunakan dalam terapi pada pasien kanker serviks karena merupakan regimen pilihan[4,5]. Meskipun demikian, sampai saat ini belum ada penelitian yang khusus membandingkan perbedaan kualitas hidup pasien setelah menjalani kemoterapi dengan kedua regimen tersebut. Melalui penelitian ini dapat diketahui bagaimana perbedaan kualitas hidup pasien setelah menjalani kemoterapi dengan dua regimen kombinasi pada sebelum dan setelah kemoterapi selama tiga siklus serta mengetahui perubahan pada masing-masing domain dengan menggunakan kuesioner EORTCQLQ-C30. Selain itu dapat diamati pula apakah terdapat perbedaan dari kedua regimen tersebut dalam dampaknya terhadap kualitas hidup. Dengan demikian dari hasil penelitian ini diharapkan diperoleh data ilmiah yang mendukung pemilihan regimen kemoterapi untuk pasien kanker serviks.

METODE

Penelitian ini merupakan studi non eksperimental bersifat analitik rancangan *cross sectional* dengan observasi lapangan. Penelitian dilakukan di RSUP Dr. Hasan Sadikin Bandung. Populasi adalah pasien kanker serviks rawat inap RSUP Dr. Hasan Sadikin Bandung. Ukuran sampel adalah berupa *total sample* yaitu seluruh pasien kanker serviks rawat inap dari bulan Juni 2015 sampai Maret 2016 yang memenuhi kriteria inklusi. Kriteria inklusi meliputi pasien rawat inap, diagnosis utama kanker serviks dengan atau tanpa penyakit penyerta *(comorbid)*, pasien dengan regimen PVB dan carboplatin-paklitaksel, baik untuk tujuan kuratif, kontrol, paliatif atau dalam bentuk kombinasi dengan terapi lain dan sudah selesai menjalani tiga siklus. Kriteria eksklusi adalah pasien rujukan rumah sakit lain, pasien waktu pulang meninggal dunia dan status pasien "keluar"

Tabel I. Data Demografi Pasien

	n	%
Umur dalam tahun		
<40 tahun	11	25,6
≥40 tahun	32	74,4
Tingkat pendidikan		
Lulusan SD	13	30,5
Lulusan SMP	8	18,4
Lulusan SLTA	21	48,8
Sarjana	1	2,3
Regimen		
Cisplatin-vinkristin-bleomisin (PVB)	32	74,4
Carboplatin-paklitaksel	11	25,6
Stadium		
I	11	24,8
II	24	56,4
III	6	14,1
IV	2	4,7

atas permintaan sendiri (APS), sehingga tidak sepenuhnya menjalani perawatan. Jumlah sampel yang diambil adalah total sample dari pasien kanker serviks rawat inap.

Kuesioner EORTC QLQ-C30 (*European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30*) adalah kuesioner yang digunakan untuk pengukuran kualitas hidup pasien kanker. Kuesioner ini terdiri dari 30 pertanyaan yang terbagi menjadi tiga kategori, yaitu: fungsional, gejala dan status kesehatan/kualitas hidup global. Perhitungan nilai kualitas hidup terdiri dari dua tahap yaitu menghitung *raw score* dan transformasi linear.

Cara interpretasi skor kualitas hidup berdasarkan pengukuran dengan EORTC QLQ-C30 adalah dengan mengevaluasi skor yang diperoleh. Skor minimal dari hasil pengisian kuesioner adalah 0 dan maksimal adalah 100. Skor yang lebih tinggi merepresentasikan level yang lebih baik untuk domain fungsional dan status kesehatan global, sedangkan untuk domain gejala merepresentasikan level yang lebih buruk[2]. Data yang diperoleh dianalisis dengan *paired t-test* ($p<0,05$) untuk mengevaluasi apakah ada perubahan yang bermakna antara kondisi setelah mendapatkan terapi dengan sebelum mendapatkan terapi[2].

HASIL DAN PEMBAHASAN

Karakteristik Demografi Pasien

Dari 110 pasien yang ditemui selama periode penelitian, diperoleh 43 pasien yang memenuhi kriteria inklusi dan tidak termasuk ke dalam kriteria eksklusi. Tabel I memuat data demografi pasien yang dilibatkan dalam penelitian ini. Sebagian besar pasien berada pada kelompok usia 40 tahun ke atas, dengan rata-rata usia 46,3±9,6 tahun dan berada pada kisaran 21-61 tahun. Rata-rata kelompok usia pasien mendekati rata-rata usia pasien pada penelitian sejenis di rumah sakit lain, antara lain RS Sanglah, Denpasar (pasien dengan rentang usia 46-55 tahun mencapai 41,7%)[6] dan di RS Sardjito, Yogyakarta (rata-rata usia 47,6±10,5)[8]. Sebagian besar pasien berpendidikan di bawah SLTA (48,9%), dengan demikian masih harus dilakukan pendampingan pada saat pengisian kuesioner. Hasil yang sama juga diperoleh pada penelitian di RS Dr. Sardjito, yaitu pasien dengan pendidikan di bawah SLTA mencapai 63,2%[8]. Pasien yang mendapatkan regimen

Tabel II. Rata-rata Domain Kualitas Hidup Sebelum dan Setelah Kemoterapi

Domain	Regimen									
	Cisplatin-vinkristin-bleomisin (PVB)					Carboplatin-paklitaksel				
	Sebelum kemoterapi		Setelah kemoterapi		P	Sebelum kemoterapi		Setelah kemoterapi		P
	Rata-rata	SD	Rata-rata	SD		Rata-rata	SD	Rata-rata	SD	
Fungsional										
Fisik	69,71	21,89	80,95	18,16	0,011	77,04	26,10	80,74	22,22	0,375
Peran	72,38	32,32	86,10	19,09	0,017	83,33	33,33	87,41	21,20	0,381
Emosi	74,29	20,35	98,57	5,89	0,000	77,78	30,33	96,30	7,35	0,047*
Kognitif	89,05	16,64	96,67	9,74	0,011	92,60	12,11	98,15	5,56	0,114
Sosial	74,76	19,96	79,05	18,67	0,178	90,74	14,70	94,44	11,79	0,282
Gejala										
Kelelahan	33,65	27,68	11,11	15,94	0,000	23,46	30,65	9,88	11,71	0,116
Mual dan Muntah	18,57	17,51	23,33	27,78	0,197	18,52	32,75	20,37	21,70	0,445
Nyeri	33,33	27,78	12,86	17,66	0,000	23,46	19,20	14,81	19,44	0,178
Sesak Nafas	20,48	27,44	5,71	12,75	0,003	7,41	16,90	0,00	0,00	0,103
Sulit Tidur	24,13	24,92	2,86	9,47	0,000	27,16	27,28	3,70	11,11	0,015*
Penurunan Nafsu Makan	23,33	22,21	37,14	25,27	0,009	16,67	18,63	22,22	16,67	0,257
Sembelit	20,00	28,87	2,86	12,45	0,001	19,75	27,65	0,00	0,00	0,024*
Diare	13,81	21,57	0,95	5,63	0,001	14,81	28,19	0,00	0,00	0,067
Kesulitan Keuangan	31,11	31,17	26,67	32,14	0,279	7,41	11,11	0,00	0,00	0,031*
Status Kesehatan / Kualitas Hidup Global	39,05	15,49	75,24	13,48	0,000	48,15	31,67	73,15	15,47	0,025*

kemoterapi PVB lebih banyak dibandingkan carboplatin-paklitaksel. Data ini sesuai dengan literatur bahwa pasien yang mendapatkan regimen berbasis carboplatin adalah yang tidak dapat menoleransi cisplatin[5]. Tingkat keparahan pasien dikelompokkan menjadi stadium I, II, III dan IV karena terdapat kemiripan pada tata laksana stadium tingkat A dan B. Sebagian besar pasien yang terlibat dalam penelitian ini berada pada stadium II, yaitu 56,4%. Hal ini berbeda dibandingkan dengan kondisi di RS Sanglah Denpasar[6]. Di rumah sakit tersebut sebagian besar pasien yang dilibatkan berada pada stadium IIIB yaitu 58,3%. Hal ini menunjukkan bahwa ada kecenderungan pasien di RSUP Dr. Hasan Sadikin Bandung lebih dini dalam melakukan pemeriksaan sehingga telah terdeteksi sejak stadium awal.

Hasil Pengukuran Kualitas Hidup Pasien

Tabel II mencantumkan nilai domain yang menggambarkan kualitas hidup pasien sebelum dan setelah kemoterapi berdasarkan hasil pengukuran dengan kuesioner EORTC QLQ-C30 untuk kedua regimen.

Setelah kemoterapi, pasien cenderung mengalami peningkatan fungsi fisik, meskipun yang bermakna hanya pada regimen PVB (p=0,011). Hasil ini sejalan dengan pengamatan di RSUP Dr. Sardjito. Berdasarkan hasil penelitian tersebut diperoleh hasil bahwa setelah kemoterapi dengan regimen berbasis cisplatin, cenderung terjadi peningkatan fungsi fisik, meskipun tidak bermakna[8]. Hasil penelitian pada kombinasi carboplatin-paklitaksel di RS Sanglah Denpasar menunjukkan peningkatan fungsi fisik secara bermakna[6].

Pemberian kemoterapi menimbulkan efek samping berupa kelelahan[9] sehingga pasien tidak dapat melakukan aktivitas dalam menjalankan perannya. Berdasarkan hasil penelitian ini, terjadi peningkatan nilai fungsi peran meskipun hanya pada regimen PVB yang bermakna (p=0,017). Peningkatan fungsi peran berkaitan dengan meningkatnya fungsi fisik dan kecenderungan menurunnya sebagian besar gejala setelah kemoterapi. Kedua hal tersebut menyebabkan pasien merasa lebih nyaman sehingga dapat kembali berperan, baik dalam kehidupan keluarga maupun di lingkungan tempat tinggalnya.

Sebelum menjalani kemoterapi, pasien merasakan khawatir, tegang dan depresi akibat penyakit yang dideritanya dan kemoterapi yang akan dijalani. Setelah kemoterapi, pasien secara psikologis berada dalam kondisi telah menerima keadaan bahwa dirinya menderita kanker dan menyadari bahwa kemoterapi memang dibutuhkan. Hal ini menyebabkan kondisi emosi menjadi lebih baik yang dinyatakan dengan peningkatan nilai domain emosi yang bermakna. Regimen PVB dan carboplatin-paklitaksel meningkatkan nilai fungsional emosi secara bermakna masing-masing dengan nilai p=0,000 dan p=0,047. Evaluasi pengaruh regimen cisplatin dan kombinasinya di RSUP Dr. Sardjito juga menunjukkan kecenderungan kenaikan fungsi emosi namun tidak bermakna[8].

Kemoterapi dapat menurunkan fungsi kognitif akibat rasa cemas[10] dan karena efek myelosupresi[11]. Berdasarkan penelitian ini teramati bahwa setelah kemoterapi, cenderung terjadi peningkatan fungsi kognitif pada kedua regimen dan bermakna pada regimen PVB (p=0,011). Carboplatin menimbulkan myelosupresi yang lebih berat dibandingkan kemoterapi lain[11]. Meskipun efek samping myelosupresi dari carboplatin menyebabkan masalah pada kognitif, namun berdasarkan hasil penelitian ini, tidak terjadi penurunan. Hal ini karena kepada pasien diberikan vitamin B6. Vitamin B6 diperlukan pada proses pembentukan sel darah merah yang berfungsi menghantarkan oksigen termasuk ke sel-sel otak agar fungsi kognitif berjalan dengan baik[12].

Pengaruh kemoterapi cenderung menurunkan nilai fungsi sosial karena pasien sedang menjalani perawatan dan harus menjalani istirahat total sehingga aktivitas sosial cenderung terganggu. Berdasarkan penelitian ini, tidak terjadi perubahan bermakna setelah mendapatkan kemoterapi dengan kedua regimen tersebut. Hasil ini sejalan dengan penelitian di India[13].

Kelelahan adalah gejala umum yang dialami akibat pemberian kemoterapi karena efek samping myelosupresi yang menimbulkan anemia[11]. Kedua regimen menunjukkan kecenderungan penurunan gejala kelelahan setelah kemoterapi dan bermakna pada regimen PVB (p=0,000). Penelitian di RSUP Dr. Sardjito pada regimen berbasis cisplatin juga menunjukkan terjadinya penurunan gejala kelelahan secara bermakna[8]. Penurunan gejala diduga karena penanganan anemia dengan suplemen zat besi dan vitamin B kompleks atau transfusi darah. Selain itu pada penderita juga terjadi penurunan sebagian besar gejala sehingga gejala sulit tidur menjadi menurun yang berdampak menurunkan gejala kelelahan. Penurunan gejala ini juga teramati pada regimen carboplatin-paklitaksel meskipun tidak bermakna.

Kemoterapi menimbulkan efek samping mual dan muntah. Hal ini disebabkan oleh stimulasi pada reseptor di saluran cerna dan *chemoreceptors trigger zone* (CTZ) yang mengirim pesan ke nukleus

traktur solitaries pada otak sehingga merangsang salivasi, kontraksi diafragma, otot pernafasan dan otot perut[14]. Pada penelitian ini, tidak terjadi perubahan bermakna pada gejala mual dan muntah meskipun menunjukkan kecenderungan peningkatan. Hal ini diduga disebabkan penggunaan antiemetik ondansetron. Berdasarkan hasil penelitian di India terbukti bahwa ondansetron menekan efek mual dan muntah yang merupakan efek samping cisplatin[15].

Nyeri tidak hanya disebabkan oleh kanker tapi juga merupakan efek samping kemoterapi[16]. Berdasarkan penelitian ini, terdapat kecenderungan penurunan nyeri setelah kemoterapi dan bermakna pada regimen PVB (p=0,000). Hal ini sejalan dengan hasil penelitian pada regimen berbasis cisplatin di RSUP Dr. Sardjito[8] dan regimen BOMP di RS Sanglah[6,7]. Penurunan gejala nyeri pada pasien diduga karena pemberian analgetik.

Obat kemoterapi, misalnya cisplatin, dapat menimbulkan gangguan pernafasan karena efek bronkokonstriksi sehingga menimbulkan sesak nafas[17]. Penanganan efek ini adalah dengan pemberian obat β2 adrenergik seperti efinefrin atau dengan glukokortikoid[18]. Pada kedua regimen ini, gejala tersebut cenderung menurun meskipun yang bermakna hanya pada regimen PVB (p=0,003). Demikian pula pada penelitian di RSUP Dr. Sardjito, cenderung terjadi penurunan gejala sesak nafas meskipun tidak bermakna[8].

Nyeri karena kanker dan efek samping dari kemoterapi dapat menimbulkan gangguan tidur[19]. Berdasarkan hasil penelitian ini, setelah kemoterapi terjadi penurunan gejala sulit tidur baik pada regimen PVB (p=0,000) maupun carboplatin-paklitaksel (p=0,015). Hasil ini sejalan dengan penelitian di RS Sanglah pada regimen BOMP[7] dan carboplatin-paklitaksel[6].

Kemoterapi berefek neurologis yang berdampak pada terjadinya sembelit[20] dan diatasi dengan pencahar seperti bisakodil. Hasil penelitian ini menunjukkan bahwa terjadi penurunan gejala sembelit yang bermakna pada regimen PVB (p=0,001) dan carboplatin-paklitaksel (p=0,024).

Kemoterapi menimbulkan ulser mukosa sehingga menyebabkan diare. Gejala ini diatasi dengan pemberian antidiare[21]. Setelah kemoterapi, terjadi kecenderungan penurunan gejala diare dan bermakna pada pasien dengan regimen PVB (p=0,001). Hasil yang sejalan dengan penelitian ini adalah pada pengamatan di RSUP Dr. Sardjito. Pasien dengan regimen berbasis cisplatin mengalami penurunan gejala diare bermakna[8].

Tingginya biaya terapi[1] dapat meningkatkan kesulitan keuangan pada pasien. Hasil menunjukkan bahwa terjadi kecenderungan penurunan kesulitan keuangan setelah kemoterapi dan bermakna pada regimen carboplatin-paklitaksel (p=0,031). Hal ini karena adanya jaminan kesehatan yang menanggung biaya pengobatan sehingga secara psikologis dapat meringankan beban keuangan. Hal ini juga teramati pada penelitian di RS Sanglah yaitu penurunan bermakna pada regimen carboplatin-paklitaksel[6]. Hasil yang berbeda terjadi pada penelitian di RSUP Dr. Sardjito. Berdasarkan hasil penelitian tersebut, terjadi peningkatan gejala keuangan bermakna pada regimen berbasis cisplatin[8]. Perbedaan ini diduga karena penelitian tersebut tidak dikhususkan pada pasien yang mendapatkan jaminan kesehatan.

Terjadi peningkatan bermakna pada domain status kesehatan / kualitas hidup global, baik pada regimen PVB (p=0,000) maupun carboplatin-paklitaksel (p=0,025). Hal ini karena kecenderungan penurunan pada hampir semua gejala. Hasil ini sejalan dengan penelitian di RS Sanglah. Berdasarkan hasil penelitian tersebut, pada regimen BOMP terjadi kecenderungan peningkatan domain tersebut meskipun tidak bermakna[7], sedangkan pada regimen carboplatin-paklitaksel terjadi peningkatan bermakna[6].

Tabel 3 mencantumkan data selisih nilai domain untuk kedua regimen pada sebelum dan setelah kemoterapi. Uji statistik terhadap

Tabel III. Selisih Domain Kualitas Hidup Sebelum dan Setelah Kemoterapi

Domain	Regimen				p
	Cisplatin-vinkristin-bleomisin		Carboplatin-paklitaksel		
	Rata-rata	SD	Rata-rata	SD	
Fungsional					
Fisik	13,33	21,14	12,39	39,49	0,210
Peran	15,62	25,79	13,21	45,37	0,164
Emosi	25,71	23,71	24,57	32,98	0,091
Kognitif	10,00	19,05	13,97	30,76	0,077
Sosial	5,71	15,63	12,69	29,92	0,278
Gejala					
Kelelahan	-20,63	21,75	-9,15	26,63	0,150
Mual dan Muntah	-2,86	32,21	5,34	41,85	0,272
Nyeri	-19,84	24,38	-3,96	27,20	0,328
Sesak Nafas	-13,81	25,72	-6,10	15,41	0,410
Sulit Tidur	-20,00	22,83	-17,85	32,15	0,444
Penurunan Nafsu Makan	14,76	28,80	8,10	25,38	0,151
Sembelit	-15,24	21,23	-16,16	25,99	0,162
Diare	-10,95	20,98	-12,12	25,92	0,353
Kesulitan Keuangan	-3,17	16,95	- 6,06	10,38	0,281
Status Kesehatan / Kualitas Hidup Global	37,14	18,34	28,51	32,99	0,411

selisih nilai domain antar regimen menunjukkan bahwa tidak terdapat perbedaan bermakna. Hal ini berarti tidak terdapat perbedaan bermakna dari kedua regimen terhadap kualitas hidup pasien. Hasil tersebut sejalan dengan hasil penelitian di Austria[22].

KESIMPULAN

Setelah kemoterapi selama tiga siklus, nilai domain baik pada pasien dengan regimen PVB maupun carboplatin-paklitaksel, terjadi kecenderungan peningkatan pada fungsional, penurunan pada gejala dan peningkatan pada status kesehatan/kualitas hidup global, kecuali pada gejala mual dan muntah serta penurunan nafsu makan yang menunjukkan kecenderungan peningkatan. Pada pasien dengan regimen PVB terjadi peningkatan bermakna (p=0,009) pada penurunan nafsu makan. Tidak terdapat perbedaan bermakna pada kualitas hidup pasien dengan regimen PVB dibandingkan dengan regimen carboplatin-paklitaksel.

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JMPF Vol. 10 No. 3 : 176-185
ISSN-p : 2088-8139
ISSN-e : 2443-2946

Evaluasi Perencanaan Persediaan Antibiotik Secara Kuantitatif di Instalasi Farmasi Rumah Sakit Tipe A

Quantitative Evaluation of Antibiotics Inventory Planning in Type A Hospital's Pharmacy Department

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ABSTRAK

Perencanaan persediaan antibiotik yang tidak baik akan menyebabkan terjadinya masalah dalam perencanaan yaitu adanya kelebihan stok antibiotik (*stagnant*) dan kekurangan stok antibiotik (*stockout*). Pada penelitian ini dilakukan evaluasi persediaan antibiotik secara kuantitatif dengan menggunakan metode *Economic Order Quantity* (EOQ) dan *Maximum-Minimum Stock Level* (MMSL) berdasarkan data penggunaan antibiotik tahun 2017 di Instalasi Farmasi Rumah Sakit tipe A di Indonesia. Metode EOQ bertujuan untuk meminimalkan jumlah pesanan sedangkan metode MMSL digunakan untuk menentukan stok minimum dan stok maksimum antibiotik yang harus dipesan. Hasil tersebut dibandingkan dengan kebutuhan pada tahun 2018 kemudian dilakukan perhitungan untuk menentukan jumlah antibiotik yang *stagnant* dan *stockout*. Jumlah antibiotik yang *stagnant* dengan simulasi metode EOQ adalah 44,73% dan dengan metode MMSL 48,02%, sedangkan jumlah antibiotik yang *stockout* dengan metode EOQ yaitu 38,15% dan dengan metode MMSL 42,76%. Kategori persediaan antibiotik pada tahun 2018 secara riil yang termasuk dalam keadaan *stagnant* adalah 23,68%, *stockout* yaitu 55,26% dari 152 antibiotik. Hasil evaluasi perencanaan persediaan antibiotik dengan metode EOQ dan MMSL dapat mengurangi jumlah antibiotik *stockout* tetapi tidak mengurangi antibiotik *stagnant*. Diperlukan penelitian lebih lanjut dengan mengikutsertakan seluruh jenis obat dan alat kesehatan yang ada di Instalasi Farmasi untuk dapat menentukan evaluasi perencanaan dengan metode pengendalian persediaan perbekalan farmasi yang paling sesuai untuk rumah sakit tipe A di Indonesia.
Kata kunci: Evaluasi perencanaan; EOQ; MMSL; *stagnant*; *stockout*

ABSTRACT

Planning an inventory of antibiotics that are not good will cause problems in planning, which are over-supply of antibiotics (stagnant) and lack of antibiotic stock (stockout). In this study a quantitative evaluation of antibiotic inventory planning was carried out using the Economic Order Quantity (EOQ) and Maximum-Minimum Stock Level (MMSL) control methods in 2017 at Type A Hospital's Pharmacy Department. The EOQ method aims to minimize the number of orders while the MMSL method is used to determine the minimum and maximum stock of antibiotics that must be ordered. The results were compared with the need for 2018 then calculations are carried out to determine the amount of stagnant and stockout antibiotics. The number of antibiotics that were stagnant by EOQ method simulation was 44.73% and by MMSL method was 48.02%, while the number of antibiotics stocked by EOQ method was 38.15% and by MMSL method was 42.76%. The category of antibiotic supplies in 2018 in real terms which was included in a stagnant state was 23.68%, stockout i.e. 55.26% of 152 antibiotics. Evaluation of antibiotic inventory planning using the EOQ method results in the calculation of lower order quantities while the number of orders with MMSL is higher. To find out more broadly about the evaluation of inventory planning in the hospital needed further research by taking into account all drugs not just antibiotics.
Keywords: Planning Evaluation; EOQ; MMSL; stagnant; stockout

PENDAHULUAN

Antibiotik sangat banyak digunakan dalam pengobatan infeksi di dalam rumah sakit. Penggunaan antibiotik sangat ditunjang dengan ketersediaan antibiotik di rumah sakit, terutama karena rumah sakit dalam penelitian ini merupakan rumah sakit kelas A yang permintaan penggunaan antibiotiknya sangat

tinggi. Jumlah persediaan antibiotik yang tidak mencukupi kebutuhan persediaan dapat menjadi salah satu penyebab terjadinya resistensi antibiotik pada pasien.

Perencanaan merupakan dasar tindakan untuk menentukan kebutuhan yang diperlukan untuk periode yang akan datang. Perencanaan sangat penting dilakukan untuk menjamin terpenuhinya kriteria tepat jenis, tepat jumlah, tepat waktu dan efisien[1]. Faktor yang mempengaruhi perencanaan obat adalah epidemiologi penyakit, efektivitas obat terhadap penyakit dan harga obat[2]. Tujuan dari perencanaan adalah untuk mendapatkan jenis dan jumlah antibiotik sesuai kebutuhan pelayanan serta untuk meningkatkan penggunaan antibiotik secara rasional. Perencanaan persediaan yang baik akan menghindari terjadinya masalah yang menyebabkan tidak efisiennya pemanfaatan antibiotik di rumah sakit.

Masalah yang sering terjadi dalam perencanaan persediaan adalah kelebihan persediaan obat (*stagnant*) dan kekurangan persediaan obat (*stockout*)[3]. Obat *stagnant* adalah sisa obat pada akhir bulan lebih dari tiga kali rata-rata pemakaian obat per bulan. *Stockout* adalah keadaan ketika jumlah sisa persediaan kurang dari pemakaian rata-rata[4].

Evaluasi perencanaan persediaan dilakukan dengan menggunakan metode pengendalian agar perencanaan yang diadakan dapat optimal[5]. Penelitian ini menggunakan metode pengendalian persediaan secara kuantitatif yaitu EOQ (*Economic Order Quantity)* dan MMSL (*Maximum-Minimum Stock Level*). Metode EOQ memerlukan dua jenis biaya yang untuk perhitungan yaitu biaya pemesanan (*ordering cost*) dan biaya penyimpanan (*holding cost*). Biaya penyimpanan (*holding cost*) adalah biaya yang dikeluarkan yang berhubungan dengan diadakannya persediaan barang yaitu biaya listrik (lampu, kulkas, AC) dan biaya sumber daya manusia[5]. Biaya pemesanan adalah biaya setiap kali dilakukan pemesanan obat antara lain biaya telepon, biaya administrasi dan biaya sumber daya manusia. Metode MMSL menentukan stok minimum dan stok maksimum persediaan dengan memperhatikan *lead time*, *consumption average*, *safety stock* dan periode pengadaan.

State of the art dari penelitian ini yaitu menghitung persediaan farmasi yang diperlukan serta memperhitungkan jumlah obat yang termasuk dalam kategori persediaan *stagnant* maupun *stockout* berdasarkan metode EOQ dan MMSL. Pada penelitian sebelumnya[6], metode EOQ dan MMSL hanya digunakan untuk menghitung persediaan farmasi yang diperlukan namun tidak memperhitungkan jumlah obat yang *stagnant* dan *stockout*. Selain itu, terdapat penelitian lain dimana dilakukan penentuan faktor penyebab stagnant dan stockout namun tidak menggunakan metode EOQ dan MMSL (Mellen pudjirahardjo) sehingga diharapkan penelitian ini memberi gambaran yang lebih jelas mengenai obat yang *stagnant* dan *stockout* yang didapatkan dari perhitungan metode EOQ dan MMSL.

Tidak adanya perhitungan jumlah obat *stagnant* dan *stockout* dapat menyulitkan tenaga kesehatan dalam melakukan pengadaan sediaan farmasi untuk periode selanjutnya. Oleh karena itu, dilakukan evaluasi perencanaan persediaan antibiotik di Instalasi Farmasi Rumah Sakit tipe A dengan menggunakan metode pengendalian persediaan EOQ dan MMSL untuk menentukan jumlah pengendalian persediaan pada tahun 2017 dan 2018 serta untuk mengetahui pendistribusian antibiotik dan untuk mengetahui adanya *stagnant* dan *stockout* persediaan sehingga dapat digunakan sebagai pertimbangan perencanaan antibiotik selanjutnya di rumah sakit.

METODE

Jenis penelitian yang dilakukan adalah studi observasional dan pengambilan data dilakukan secara retrospektif pada tahun 2017 dan 2018. Penelitian ini hanya dilakukan pada satu rumah sakit tipe A di Indonesia dan dilakukan dengan menggunakan kartu stok pada semua sampel antibiotika di Gudang Instalasi Farmasi Rumah Sakit. Penelitian mengenai evaluasi perencanaan persediaan

antibiotik dilakukan secara kuantitatif dengan menggunakan metode pengendalian persediaan EOQ dan MMSL. Kriteria inklusi pada penelitian ini adalah antibiotik yang tercatat keluar dari gudang IFRS baik pada bulan Januari-Desember 2017 maupun pada bulan Januari-Desember 2018 sedangkan kriteria eksklusi pada penelitian ini adalah data pengeluaran antibiotik yang tidak lengkap.

Perhitungan pengendalian persediaan antibiotik pada tahun 2017 dan 2018 dengan metode EOQ dihitung dengan menggunakan rumus:

$$EOQ = \sqrt{\frac{2DS}{H}}$$

Keterangan: EOQ : jumlah pemesanan yang meminimalkan biaya persediaan; D = jumlah kebutuhan barang (unit/tahun); S = biaya pemesanan yang ditentukan dari kuantitas pemesanan; H = biaya penyimpanan dengan satuan rupiah/unit/tahun

Perhitungan pengendalian persediaan antibiotik pada tahun 2017 dan 2018 dengan metode MMSL dihitung dengan menggunakan rumus :

$$Smin = (LT \times CA) + SS = 2SS$$
$$Smaks = Smin + (PP \times CA)$$

Keterangan: Smin = stok minimal; Smaks = stok maksimum; CA = *consumption average* atau rata-rata pemakaian setiap bulan; LT = *lead time;* PP = periode pengadaan; SS = *safety stock* atau stok pengaman (LT x CA)

Kemudian dilakukan perhitungan jumlah antibiotik yang masuk dalam kategori *stagnant* dan *stockout* pada tahun 2018 baik keadaan riil maupun dengan metode EOQ dan MMSL. Untuk menentukan kategori persediaan antibiotik, maka harus dilakukan perhitungan sisa stok pada setiap metode. Sisa stok pada metode EOQ dapat dihitung dengan rumus :

$$\text{Sisa stok} = (\text{pembelian EOQ} \times \text{frekuensi pembelian}) + \text{stok awal} - \text{pemakaian(tahun)}$$

Keterangan: Pembelian EOQ = jumlah pemesanan yang dihitung dengan metode EOQ tahun 2017; Frekuensi pembelian = $\frac{pemakaian\ (tahun)}{pembelian\ EOQ}$; Stok awal = stok awal pada bulan Januari tahun 2018; Pemakaian (tahun) = jumlah pemakaian antibiotik selama 1 tahun

Sisa stok pada metode MMSL dapat dihitung dengan rumus :

$$\text{Sisa stok} = (\text{pembelian MMSL} \times \text{frekuensi pembelian}) + \text{stok awal} - \text{pemakaian(tahun)}$$

Keterangan: Pembelian MMSL = jumlah pemesanan yang dihitung dengan metode MMSL tahun 2017; Frekuensi pembelian = jumlah pengadaan dalam 1 tahun (dapat diketahui dari periode pengadaan); Stok awal = stok awal pada bulan Januari tahun 2018; Pemakaian (tahun) = jumlah pemakaian antibiotik selama 1 tahun

Setelah diketahui sisa stok dengan masing-masing metode, maka dapat ditentukan kategori persediaan antibiotik dengan melihat sisa stok dengan pemakaian rata-rata per bulan. Antibiotik dikatakan *stagnant* bila sisa stok lebih dari tiga kali pemakaian rata-rata per bulan sedangkan antibiotik yang dikatakan *stockout* bila sisa stok kurang dari pemakaian rata-rata per bulan. Antibiotik dikatakan memiliki kategori persediaan normal apabila sisa obat tidak kurang dari pemakaian rata-rata per bulan dan tidak lebih dari tiga kali pemakaian rata-rata per bulan.

HASIL DAN PEMBAHASAN

Dari data pengeluaran antibiotik pada periode bulan Januari-Desember 2017 dan Januari-Desember 2018 didapatkan 152 antibiotik yang memenuhi kriteria inklusi dan 65 antibiotik tidak memenuhi kriteria inklusi karena hanya ada di salah satu yaitu tahun 2017 atau 2018 saja sehingga tidak dapat dilakukan komparasi (Tabel I).

Perhitungan Pengendalian Persediaan Antibiotik dengan Metode EOQ

Hasil penelitian pada tabel II menunjukkan biaya yang dikeluarkan akibat adanya penyimpanan dan biaya pemesanan obat di gudang. Total biaya yang dikeluarkan untuk biaya penyimpanan pada tahun 2017 yaitu sebesar IDR 516. Biaya penyimpanan

Tabel I. Total Antibiotik dan Bentuk Sediaan Antibiotik di Instalasi Farmasi Rumah Sakit Tipe A pada Tahun 2017-2018

Total Jenis Antibiotik	Bentuk Sediaan
217 jenis antibiotik - 152 jenis masuk kriteria inklusi - 65 jenis antibiotik masuk kriteria eksklusi	Tablet, kapsul, kaplet, sirup, injeksi, suppositoria, salep dan obat tetes

Tabel II. Biaya Penyimpanan dan Biaya Pemesanan per Unit Barang di Instalasi Farmasi Rumah Sakit Tipe A pada Tahun 2017-2018

Jenis Biaya	Biaya (IDR)/Unit/Tahun
Biaya Penyimpanan	516
Biaya Pemesanan	30.209

yang dihasilkan pada penelitian ini lebih tinggi bila dibandingkan dengan penelitian lain di RSUD Cicalengka yaitu IDR 0,5-145[7]. Bila dibandingkan dengan penelitian lain di Rumah Sakit Paru Jember, biaya penyimpanan yang dihasilkan lebih tinggi yaitu IDR 48.729[8]. Perbedaan pada kedua penelitian tersebut dapat disebabkan karena perbedaan tipe rumah sakit sehingga kebutuhan obat di setiap rumah sakit berbeda. Selain itu, hal yang menyebabkan perbedaan biaya penyimpanan yaitu harga setiap obat dan biaya persediaan di rumah sakit. Semakin besar harga obat maka biaya penyimpanan juga akan semakin besar begitu juga sebaliknya[9].

Total biaya pemesanan yang dikeluarkan adalah IDR 30.209 untuk setiap kali pemesanan. Hasil biaya pemesanan yang dilakukan di Rumah Sakit Paru Jember memiliki biaya yang sedikit lebih rendah yaitu IDR 29.355[8]. Hal ini dapat disebabkan karena pada penelitian tersebut memperhitungkan biaya kertas, tinta printer dan telepon sedangkan pada penelitian ini biaya pemesanan memperhitungkan biaya kertas, telepon, internet, tinta printer dan biaya sumber daya manusia sehingga memberikan hasil yang lebih besar. Pada penelitian lain yang dilakukan di RSUD Cicalengka, biaya pemesanan yang dihasilkan yaitu IDR 9-4.291[7]. Salah satu hal yang menyebabkan adanya perbedaan biaya pemesanan adalah jumlah obat dan frekuensi pemesanan yang diperhitungkan tidak sama sehingga memberi hasil yang berbeda. Hal ini sesuai dengan teori dimana biaya pemesanan per periode didapatkan dari frekuensi pesanan dikalikan dengan biaya setiap kali pesan[10]. Selain itu, perbedaan rumah sakit akan mempengaruhi biaya pemesanan yang dilakukan karena jumlah obat yang digunakan di setiap rumah sakit pasti berbeda.

Berdasarkan hasil perhitungan biaya penyimpanan dan biaya pemesanan maka dapat dilakukan perhitungan pengendalian persediaan pada tahun 2017 dan 2018 dengan metode EOQ. Metode EOQ adalah metode yang digunakan untuk menentukan jumlah pesanan yang ekonomis setiap kali dilakukan pemesanan[8]. Metode ini memperhitungkan biaya penyimpanan, jumlah kebutuhan antibiotik dan biaya pemesanan. Data yang digunakan adalah data pengeluaran antibiotik pada tahun 2017 dan 2018 sebagai *demand* untuk melihat hasil perhitungan pengendalian persediaan antibiotik dengan metode EOQ. Dalam penelitian ini, biaya pemesanan dan biaya penyimpanan dianggap sama setiap antibiotik sehingga hasil EOQ yang berbeda-beda dipengaruhi oleh jumlah kebutuhan antibiotik (D) yang tidak sama setiap antibiotik.

Pada tabel III dapat dilihat perhitungan pengendalian persediaan antibiotik dengan metode EOQ pada tahun 2017 dan 2018 dimana data hanya ditampilkan 5 antibiotik dengan EOQ terbesar dari total keseluruhan antibiotik. Antibiotik dengan EOQ terbesar

Tabel III. Hasil Perhitungan Pengendalian Persediaan Antibiotik di Instalasi Farmasi Rumah Sakit Tipe A pada Tahun 2017 dan 2018 dengan metode EOQ)*

Tahun	Nama Sediaan Antibiotik	Jumlah Pengeluaran 1 tahun (D)	Biaya Penyimpanan (H)	Biaya Pemesanan (S)	EOQ (unit)
Tahun 2017	Seftriakson 1 gram Inj	97.387	516	30.209	3.377
	Metronidazol 500 mg	68.800	516	30.209	2.838
	Sefiksim 100 mg	68.000	516	30.209	2.822
	Framisetin Sulfat	60.590	516	30.209	2.644
	Siprofloksasin 500 mg	37.400	516	30.209	2.093
	Total	**332.177**			**13.774**
Tahun 2018	Framisetin Sulfat	89.580	516	30.209	3.239
	Sefiksim 100 mg kapsul	82.005	516	30.209	3.099
	Seftriakson 1 g Inj	62.064	516	30.209	2.696
	Amoksisilin 500 mg	39.200	516	30.209	2.142
	Amoksisilin 500 mg kaplet	37.100	516	30.209	2.084
	Total	**309.949**			**13.260**

pada tahun 2017 adalah seftriakson 1 gram injeksi dengan kuantitas pemesanan 3.377 unit sedangkan antibiotik dengan EOQ terendah adalah siprofloksasin 500 mg dengan kuantitas pemesanan 2.093 unit sedangkan pada tahun 2018 antibiotik dengan EOQ terbesar adalah framisetin sulfat dengan kuantitas pemesanan 3.239 dan antibiotik dengan EOQ terendah adalah amoksisilin 500 mg kaplet dengan kuantitas pemesanan 2.084 unit. Jumlah perhitungan pengendalian persediaan 5 antibiotik dengan metode EOQ pada tahun 2017 adalah 13.774 unit sedangkan pada tahun 2018 berjumlah 13.260 unit antibiotik. Hasil EOQ yang berbeda dipengaruhi oleh jumlah kebutuhan antibiotik yang berbeda pada tahun 2017 dan 2018. Semakin besar jumlah pengeluaran antibiotik, maka EOQ yang dihasilkan juga semakin besar. Perbedaan EOQ yang dihasilkan sejalan dengan penelitian di RSUD Cicalengka dimana setiap antibiotik memberikan hasil EOQ yang berbeda[7]. Selain itu, penelitian di Rumah Sakit Meilia memberi hasil EOQ yang berbeda untuk setiap obat[11]. Pada penelitian di Rumah Sakit PKU Aisyiyah Boyolali juga menghasilkan perbedaan EOQ pada setiap obat yang dihitung[12]. Hal ini disebabkan karena adanya perbedaan jumlah kebutuhan obat, biaya penyimpanan dan biaya pemesanan yang berbeda-beda setiap rumah sakit. Namun dengan metode EOQ maka jumlah pesanan dan biaya persediaan dapat berkurang[7]. Selain itu, metode EOQ dapat digunakan untuk mengurangi kemungkinan adanya obat yang kadaluarsa[13] serta dapat meminimalkan biaya penyimpanan serta stok yang berlebihan[14].

Perhitungan Pengendalian Persediaan Antibiotik dengan Metode MMSL

Metode MMSL digunakan untuk mengatur jadwal pengadaan yang memberikan interval waktu pemesanan untuk menentukan jumlah stok minimum dan maksimum yang sesuai untuk persediaan obat agar tidak terjadi kekosongan maupun kelebihan obat[15]. Berdasarkan data yang didapatkan dengan wawancara kepala gudang Instalasi Farmasi di rumah sakit, *lead time* yang digunakan adalah 14 hari atau 0,5 bulan. *Lead time* adalah jarak waktu tunggu dari awal pemesanan sampai obat datang dan siap digunakan[16]. Bila *lead time* yang digunakan tidak menentu maka dapat meningkatkan safety stock[17]. *Lead time* sangat penting karena berhubungan dengan penentuan waktu pemesanan yang dilakukan

Tabel IV. Hasil Perhitungan Pengendalian Persediaan Antibiotik di Instalasi Farmasi Rumah Sakit Tipe A pada Tahun 2017 dan 2018 dengan metode MMSL

Tahun	Nama Sediaan Antibiotik	Safety Stock (unit)	Pengeluaran Rata-rata per bulan (unit)	S_{min} (unit)	S_{max} (unit)	Jumlah Pesan
Tahun 2017	Seftriakson 1 gram Inj	4.058	8.115	8.115	32.462	24.347
	Metronidazol 500 mg	2.867	5.733	5.733	22.933	17.200
	Sefiksim 100 mg	2.833	5.667	5.667	22.667	17.000
	Framisetin Sulfat	2.525	5.049	5.049	20.197	15.148
	Siprofloksasin 500 mg	1.558	3.117	3.117	12.467	9.350
	Total	**13.841**	**27.721**	**27.721**	**110.726**	**83.045**
Tahun 2018	Framisetin Sulfat	3.733	7.465	7.465	29.860	22.395
	Sefiksim 100 mg kapsul	3.417	6.834	6.834	27.335	20.501
	Seftriakson 1 g Inj	2.586	5.172	5.172	20.668	15.516
	Amoksisilin 500 mg	1.633	3.267	3.267	13.067	9.800
	Amoksisilin 500 mg kaplet	1.545	3.092	3.092	12.367	9.275
	Total	**12.914**	**25.830**	**25.830**	**103.297**	**77.487**

kembali[18]. *Safety stock* atau stok pengaman adalah persediaan yang dilakukan untuk mengantisipasi ketidakpastian permintaan dan persediaan[19]. *Safety stock* didapatkan dengan memperhitungkan *lead time* dan pemakaian rata-rata tiap antibiotik. Stok minimum didapatkan dari rata-rata pemakaian dikalikan dengan *lead time* ditambahkan dengan stok pengaman. Stok maksimum dapat ditentukan dari jumlah stok minimum ditambahkan dengan periode pengadaan dikalikan dengan rata-rata pemakaian[2]. Periode pengadaan yang terjadwal ditetapkan setiap 3 bulan sekali. Periode pengadaan dan *lead time* untuk setiap jenis antibiotik dianggap sama.

Hasil penelitian pada tabel IV menunjukkan perhitungan pengendalian persediaan antibiotik tahun 2017 dan tahun 2018 dengan metode MMSL. Sama dengan metode EOQ, pada metode MMSL data ditampilkan 5 antibiotik dengan jumlah pesan terbesar. Antibiotik dengan jumlah pesan terbesar pada tahun 2017 adalah seftriakson 1 gram injeksi dengan jumlah pemesanan 24.347 unit sedangkan antibiotik dengan jumlah pesan terendah adalah siprofloksasin 500 mg dengan jumlah pemesanan 9.350 unit sedangkan pada tahun 2018 antibiotik dengan MMSL terbesar adalah framisetin sulfat dengan jumlah pemesanan 22.395 dan antibiotik dengan MMSL terendah adalah amoksisilin 500 mg kaplet dengan jumlah pemesanan 9.275 unit. Jumlah perhitungan pengendalian persediaan 5 antibiotik dengan metode MMSL pada tahun 2017 adalah 83.045 unit sedangkan pada tahun 2018 berjumlah 77.487 unit antibiotik.

Penelitian ini sejalan dengan penelitian di Rumah Sakit Islam Surabaya dimana setiap obat menghasilkan jumlah pesanan yang berbeda[15]. Selain itu, penelitian yang dilakukan di RSUP Dr. Sardjito juga memberikan hasil jumlah pesanan yang berbeda meskipun periode pengadaan yang digunakan sama yaitu 3 bulan[20]. Hal ini dapat disebabkan karena jumlah pesanan bergantung juga pada *lead time*, *safety stock* dan pengeluaran rata-rata setiap antibiotik. Jumlah pesanan yang harus dilakukan dapat dihitung dengan mengurangi stok maksimum dengan stok minimum. Bila persediaan antibiotik sudah mencapai level minimum maka harus dilakukan pemesanan sebesar jumlah pesan agar tidak terjadi kekurangan stok. Pemesanan kembali dilakukan saat stok

Tabel V. Kategori Persediaan Antibiotik Secara Riil di Rumah Sakit Tipe A pada Tahun 2018, dengan Simulasi Metode EOQ dan MMSL

Kategori Persediaan	Stok Riil 2018 (unit)	EOQ (unit)	Ab pada Stok Riil dan EOQ (%)	MMSL (unit)	Ab Riil dan MMSL (%)	Ab pada EOQ dan MMSL (%)
Stagnant	36 (23,68%)	68 (44,73%)	20 (13,15%)	73 (48,02%)	22 (14,47%)	39 (25,65%)
Stockout	84 (55,26%)	58 (38,15%)	34 (22,36%)	65 (42,76%)	34 (22,7%)	35 (23,02%)
Normal	32 (21,05%)	26 (17,10%)	10 (6,57%)	14 (9,21%)	2 (1,32%)	4 (2,63%)
Total	152	152	64	152	58	78

mencapai level minimum karena stok minimum disediakan saat masa tenggang waktu (*lead time*)[15].

Kategori Persediaan Antibiotik

Kategori persediaan antibiotik baik pada metode EOQ maupun metode MMSL ada 3 yaitu *stagnant*, *stockout* dan normal. Antibiotik dikatakan *stagnant* bila sisa stok lebih dari tiga kali pemakaian rata-rata per bulan sedangkan antibiotik yang dikatakan *stockout* bila sisa stok kurang dari pemakaian rata-rata per bulan[4]. Antibiotik dikatakan memiliki kategori persediaan normal apabila sisa obat tidak kurang dari pemakaian rata-rata per bulan dan tidak lebih dari tiga kali pemakaian rata-rata per bulan.

Dalam menentukan kategori persediaan antibiotik dengan metode EOQ maka diperlukan data stok awal dan pembelian serta perhitungan frekuensi pembelian dan *Consumption Average* (CA). Stok awal didapatkan dari stok awal pada bulan Januari 2018 sedangkan pembelian EOQ didapatkan dari data pengendalian persediaan dengan metode EOQ pada tahun 2017. Dengan menggunakan data pengendalian persediaan pada tahun 2017, maka dapat dilihat kategori persediaan mana yang memberi hasil lebih baik antara riil 2018 atau dengan menggunakan metode EOQ. Frekuensi pembelian dapat ditentukan dari pemakaian per tahun dibagi dengan pembelian EOQ sedangkan pemakaian per tahun sendiri adalah jumlah pemakaian antibiotik dalam setahun. CA adalah pemakaian rata-rata per bulan yang didapat dari pemakaian per tahun dibagi 12 bulan sedangkan 3xCA adalah 3 kali pemakaian rata-rata per bulan. Sisa stok didapatkan dari pembelian EOQ dikali dengan frekuensi pembelian kemudian ditambah stok awal dan dikurangi dengan pemakaian per tahun.

Pada metode MMSL, stok awal sama dengan metode EOQ yaitu stok awal pada bulan Januari 2018. Pembelian MMSL didapatkan dari data pengendalian persediaan dengan metode EOQ dan MMSL pada tahun 2017. Dengan menggunakan data pengendalian persediaan pada tahun 2017, maka dapat dilihat kategori persediaan mana yang memberi hasil lebih baik antara riil 2018 atau dengan menggunakan metode MMSL. Frekuensi pembelian dapat ditentukan dari periode pengadaan, karena periode pengadaan dalam setahun adalah setiap 3 bulan sekali maka frekuensi pembeliannya yaitu 4 kali tiap tahun. Untuk cara perhitungan CA dan 3xCA pada metode MMSL sama dengan metode EOQ. Perhitungan sisa stok didapatkan dari pembelian MMSL dikali dengan frekuensi pembelian kemudian ditambah stok awal dan dikurangi dengan pemakaian per tahun.

Dari hasil kategori persediaan yang telah dihitung dengan metode EOQ dan MMSL, maka ditentukan kategori persediaan antibiotik yang dibandingkan dengan keadaan riil pada tahun 2018. Hasil penelitian pada tabel V menunjukkan kategori

persediaan antibiotik data riil pada tahun 2018, dengan metode EOQ dan dengan metode MMSL. Dari tabel tersebut dapat dilihat bahwa dengan perencanaan konsumsi tahun 2018, antibiotik yang masuk kategori *stagnant* yaitu 36 (23,68%) sedangkan jumlah antibiotik *stockout* yaitu 84 (55,26%) dan antibiotik stok normal yaitu sebesar 32 (21,05%) jenis antibiotik. Dengan metode pengendalian EOQ, jumlah antibiotik *stagnant* meningkat yaitu sebanyak 68 antibiotik (44,73%) namun jumlah antibiotik yang *stockout* menurun yaitu 58 (38,15%) dan antibiotik stok normal yaitu 26 (17,10%) jenis antibiotik. Dari tabel V juga dapat dilihat bahwa terdapat 20 jenis antibiotik *stagnant*, 34 jenis antibiotik *stockout* dan 10 jenis antibiotik normal yang sama baik pada data riil 2018 maupun dengan metode EOQ.

Dengan metode pengendalian MMSL, jumlah antibiotik yang *stagnant* meningkat yaitu sebanyak 73 (48,02%), antibiotik *stockout* menurun yaitu 65 (42,76%) dan antibiotik normal juga menurun menjadi 14 (9,21%) dari keadaan riil pada tahun 2018. Bila dibandingkan dengan keadaan riil 2018, jumlah antibiotik pada simulasi metode MMSL yang memiliki kategori sama adalah sebanyak 58 antibiotik dengan kategori *stagnant* 22 antibiotik, *stockout* 34 antibiotik dan normal 2 antibiotik. Pada metode EOQ dan MMSL, terdapat 78 antibiotik yang memiliki kategori sama pada kedua metode dengan jumlah obat *stagnant* 39 sedangkan obat *stockout* 25 dan obat yang normal 4. Dari hasil tersebut, diketahui bahwa lebih banyak terdapat obat *stagnant* dan *stockout* dibandingkan obat normal pada kedua metode.

Hasil penelitian ini berbeda dengan penelitian di RSU Haji Surabaya dimana jumlah jenis obat *stagnant* 118 (39%) dan jumlah jenis obat *stockout* 166 (54%)[22]. Penelitian juga berbeda dengan penelitian di rumah sakit Mata Masyarakat Jawa Timur dimana hasil penelitian obat *stagnant* sebesar 39% dan *stockout* sebesar 29% dari total 1.033 jenis obat[4]. Hal ini menunjukkan perbedaan rumah sakit dapat menyebabkan hasil jumlah obat *stagnant* dan *stockout* yang sangat berbeda. Faktor lain yang dapat menyebabkan adanya perbedaan *stagnant* dan *stockout* adalah adanya ketidaksesuaian antara jumlah stok dengan pengeluaran antibiotik setiap bulannya[5]. Pada keadaan *stockout*, proses yang terjadi di rumah sakit akan terhambat dan dapat berdampak buruk terhadap pengobatan pasien. Selain itu, banyaknya obat yang *stockout* dapat menyebabkan mutu pelayanan rumah sakit menurun bila terdapat resep yang tidak dilayani[21]. Obat yang mengalami *stagnant* memiliki risiko kadaluarsa dan kerusakan yang tinggi bila tidak disimpan dengan benar[4].

Berdasarkan hasil penelitian tabel V dapat dilihat bahwa metode EOQ dapat menurunkan antibiotik yang *stockout* lebih banyak daripada metode MMSL seperti pada penelitian di Gudang Farmasi Klinik XYZ dimana metode EOQ dapat mengoptimalkan persediaan serta menurunkan total biaya persediaan[22]. Hal ini sesuai dengan penelitian lainnya dimana metode EOQ dapat menurunkan efisiensi biaya persediaan dalam pemesanan obat[23].

Faktor yang dapat menyebabkan terjadinya antibiotik yang *stagnant* adalah adanya pengadaan yang melebihi jumlah pemakaian antibiotik[24]. Hal yang mempengaruhi terjadinya *stockout* adalah penggunaan antibiotik yang meningkat dibandingkan periode sebelumnya. Faktor lain yang dapat mempengaruhi adanya *stockout* adalah jumlah perencanaan yang tidak sesuai dengan pemakaian obat, dan *lead time* tidak sesuai prediksi[25]. Banyaknya antibiotik yang *stagnant* menunjukkan perlunya pengurangan perencanaan pada periode selanjutnya agar tidak terjadi kelebihan stok. Begitu juga sebaliknya, banyaknya antibiotik yang *stockout* menunjukkan perlunya diadakan perencanaan yang lebih banyak untuk periode selanjutnya agar tidak terjadi kekurangan stok.

Kerugian akibat obat yang *stagnant* dalam segi biaya yaitu biaya pembelian, biaya pemesanan, biaya penyimpanan dan biaya

kerusakan atau kadaluarsa. Kerugian yang akan ditanggung akibat banyaknya obat yang *stockout* adalah hilangnya *opportunity cost* atau biaya kesempatan[4]. Untuk melihat kerugian akibat terjadinya obat *stagnant* dan *stockout* dalam segi biaya dapat memperhitungkan *opportunity cost* dan *opportunity loss* yang terjadi.

Penentuan jumlah pemesanan dan perencanaan pembelian sangat penting untuk pengendalian persediaan antibiotik sehingga diperlukan jumlah pemesanan yang optimal untuk mengantisipasi adanya fluktuasi permintaan maupun kekosongan stok obat[26]. Dengan adanya perencanaan yang baik maka dapat menghindari terjadinya masalah dalam pelayanan kefarmasian serta menunjang pelayanan kesehatan di rumah sakit. Keterbatasan dalam penelitian ini yaitu tidak didapatkan biaya penyimpanan dan biaya pemesanan secara rinci dan lengkap.

KESIMPULAN

Jumlah pemesanan yang harus dilakukan agar stok antibiotik optimal dengan metode EOQ memberikan hasil yang lebih rendah sedangkan jumlah pemesanan dengan metode MMSL lebih besar. Pada keadaan riil 2018, jumlah antibiotik yang masuk kategori *stagnant* lebih rendah dibanding dengan metode EOQ dan MMSL, namun jumlah antibiotik *stockout* dengan metode EOQ dan MMSL lebih rendah daripada keadaan riil 2018 dan antibiotik stok normal dengan metode EOQ lebih tinggi dibandingkan metode MMSL. Evaluasi perencanaan dengan menggunakan metode pengendalian persediaan EOQ dapat menurunkan jumlah antibiotik *stockout* lebih banyak daripada metode MMSL.

UCAPAN TERIMA KASIH

Terimakasih kepada Direktur Rumah Sakit yang telah memberikan ijin penelitian.

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JMPF Vol. 10 No. 3 : 186-194
ISSN-p : 2088-8139
ISSN-e : 2443-2946

Evaluasi Penggunaan Aspirin Jangka Panjang terhadap Fungsi Ginjal Pasien Penyakit Jantung Koroner

Evaluation of Long-Term Use of Aspirin on Kidney Function of Coronary Heart Disease Patients

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Submitted: 09-01-2020 *Revised: 30-06-2020* *Accepted: 28-09-2020*
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ABSTRAK

Aspirin dosis-rendah (75-100 mg/hari) adalah terapi antiagregasi platelet bagi pasien penyakit jantung koroner (PJK) tertentu yang diberikan jangka panjang. Penelitian ini bertujuan untuk mengevaluasi penggunaan aspirin jangka panjang terhadap fungsi ginjal dengan melihat perubahan kadar kreatinin serum, *blood urea nitrogen* (BUN), dan klirens kreatinin pasien PJK. Metode penelitian yang digunakan yaitu analisis observasional kohort secara prospektif. Jumlah subjek penelitian yang memenuhi kriteria inklusi dan eksklusi sebanyak 37 pasien PJK pengguna aspirin dosis 80 mg/hari tanpa riwayat penyakit ginjal. Dilakukan pemeriksaan kadar kreatinin serum dan BUN pada bulan ke-1 dan bulan ke-3 dimulainya penelitian. Nilai klirens kreatinin pasien dihitung menggunakan rumus Cockcroft-Gault. Berdasarkan hasil penelitian, diperoleh rerata kadar kreatinin serum, BUN, dan klirens kreatinin pada bulan ke-1 dan bulan ke-3 masing-masing sebesar 1,03 ± 0,27 mg/dL dan 1,03 ± 0,29 mg/dL; 13,05 ± 4,10 mg/dL dan 14,65 ± 4,44 mg/dL; 73,16 ± 18,14 mL/menit dan 72,92 ± 19,76 mL/menit. Hasil uji t berpasangan menunjukan bahwa perbedaan rerata kreatinin serum, BUN, dan klirens kreatinin bulan ke-1 dan bulan ke-3 tidak signifikan secara statistik ($p > 0,05$). Hasil uji *One Way ANOVA* tentang pengaruh durasi penggunaan aspirin terhadap fungsi ginjal juga tidak signifikan secara statistik ($p > 0,05$) namun terdapat kecenderungan penurunan klirens kreatinin serta peningkatan kreatinin serum dan BUN. Penggunaan aspirin dosis-rendah dalam jangka panjang berpotensi menyebabkan penurunan fungsi ginjal jika dilihat dari adanya penurunan nilai klirens kreatinin serta peningkatan kreatinin serum dan BUN.
Kata kunci: Aspirin dosis-rendah; BUN; kreatinin serum; penyakit jantung koroner

ABSTRACT

Low-dose aspirin (75-100 mg/day) is a long-term platelet antiaggregation therapy for certain coronary heart disease (CHD) patients. This study aims to evaluate the long-term use of aspirin on kidney function by examining the changes in the levels of serum creatinine, blood urea nitrogen (BUN), and creatinine clearance of CHD patients. The research method used was a prospective observational cohort analysis. The number of study subjects was 37 CHD patients who took 80 mg/day of aspirin and never experienced kidney disease. Serum creatinine and BUN levels were examined in the 1st and 3rd month of the study. Patient creatinine clearance values were calculated using the Cockcroft-Gault equation. The results of the study showed that the mean levels of serum creatinine, BUN, and creatinine clearance on the 1st and 3rd month were 1.03 ± 0.27 mg/dL and 1.03 ± 0.29 mg/dL; 13.05 ± 4.10 mg/dL and 14.65 ± 4.44 mg/dL; 73.16 ± 18.14 mL/min and 72.92 ± 19.76 mL/min, respectively. The paired t-test results showed that the differences in the mean of creatinine serum, BUN, and creatinine clearance on the 1st and 3rd month were not statistically significant ($p > 0.05$). The One Way ANOVA test results on the effect of the duration of aspirin use on kidney function were also not statistically significant ($p > 0.05$) however there is a tendency to decrease creatinine clearance and increase in serum creatinine and BUN. Long-term use of low-dose aspirin has the potential to cause a decrease in kidney function that is seen from a decrease in creatinine clearance as well as an increase in serum creatinine and BUN.
Keywords: Low-dose aspirin; BUN; serum creatinine; coronary heart disease

PENDAHULUAN

Penyakit Jantung Koroner (PJK) merupakan penyakit kardiovaskular yang menyebabkan kematian nomor satu di Indonesia. PJK diprediksi akan terus bertambah hingga 23,3 juta dan menjadi penyebab kematian pada tahun 2030[1]. Aterosklerosis adalah alasan yang mendasari hampir semua penyebab PJK. Lesi lapisan lemak dapat berkembang menjadi plak yang rentan terhadap pecah atau erosi. Gangguan plak menginisiasi adhesi platelet dan agregasi pada permukaan vaskular yang terpapar dan aktivasi kaskade pembekuan yang mengarah pada proses aterotrombosis. Untuk itu, terapi antiagregasi platelet banyak digunakan untuk mencegah dan menghambat proses aktivasi/agregasi platelet dan aktivasi kaskade koagulasi[2].

Upaya yang dilakukan oleh tenaga kesehatan untuk meningkatkan kualitas hidup pasien PJK yaitu pemberian terapi antiagregasi platelet salah satunya dengan aspirin. Analisis-meta oleh *the Antithrombotic Trialists' Collaboration* menunjukkan bahwa pemberian aspirin dapat menurunkan kejadian vaskular serius dan menurunkan laju mortalitas pada penyakit kardiovaskular maupun serebrovaskular[3]. Respons pasien PJK di salah satu rumah sakit di Indonesia juga masih bagus karena hasil penelitian oleh Yunita dkk. (2015) membuktikan bahwa tidak ada pasien yang mengalami resistensi terhadap aspirin[4].

Aspirin bertindak sebagai agen asetilasi sehingga aspirin secara irreversibel menonaktifkan siklooksigenase (COX)-1 dan menekan pembentukan prostaglandin H2 (prekursor tromboksan A2). Aspirin menghasilkan kerusakan irreversibel dalam sintesis tromboksan untuk seumur hidup platelet yang terpapar (8-10 hari). Pemberian aspirin dosis-rendah dapat sepenuhnya menghambat COX-1 (menyebabkan efek jangka panjang) pada dosis harian yang diulang. Pencegahan yang dimediasi aspirin melibatkan penghambatan platelet. Sampai saat ini, aspirin telah dianggap sebagai obat yang mencegah trombosis arteri melalui penghambatan COX-1. Pedoman saat ini menetapkan peran aspirin dalam pencegahan primer kejadian kardiovaskular. Kejadian paling awal dalam pembentukan trombus adalah adhesi platelet diikuti oleh agregasi, aktivasi platelet, dan pelepasan granula. Kecuali untuk adhesi platelet, semua fungsi platelet ini dapat dihambat oleh aspirin. Oleh karenanya, aspirin mampu mengurangi risiko kejadian trombosis arteri[5].

Aspirin menghambat pembentukan prostaglandin H2 (PGH_2) melalui ikatan kovalen dengan Ser529 yang merupakan sisi aktif dari enzim COX-1[5]. PGH_2 diproduksi secara melimpah di ginjal. Dalam kondisi fisiologis, PGH_2 berperan penting dalam pengaturan hemodinamik ginjal, pelepasan renin, serta keseimbangan air dan garam[6]. Penelitian oleh **Sarsam dan Adeep (2009) menunjukkan bahwa aspirin dosis 300 mg/hari yang diberikan selama 4 minggu dapat menurunkan fungsi ginjal dan aspirin berpotensi menurunkan fungsi ginjal[7]. Segal *et al.*, (2006) menyatakan bahwa pemberian aspirin dosis-rendah (100 mg/hari) pada pasien lansia selama 2 minggu secara signifikan dapat memperburuk fungsi tubulus ginjal[8]. Selain itu, t**erdapat penelitian lain di Indonesia tentang pengaruh penggunaan obat anti-inflamasi non-steroid (OAINS) pada fungsi ginjal pasien osteoartritis dengan durasi terapi minimal 4 minggu. Berdasarkan penelitian tersebut didapatkan hasil bahwa penggunaan OAINS selama 4-8 minggu dapat meningkatkan kreatinin serum dan BUN (*blood urea nitrogen*) pada pasien yang berusia > 60 tahun. Efek penggunaan aspirin jangka panjang terkait fungsi ginjal terutama pada pasien lansia memerlukan perhatian khusus[8,9]. Oleh karenanya, dilakukan penelitian ini untuk mengetahui pengaruh penggunaan aspirin dosis-rendah dalam jangka panjang terhadap fungsi ginjal pada pasien PJK karena belum banyak penelitian di Indonesia yang mengevaluasi tentang efek ini.

METODE

Desain penelitian

Penelitian ini merupakan studi observasional kohort prospektif karena peneliti mengikuti subjek penelitian selama 3 bulan untuk melakukan pemeriksaan laboratorium dari sampel darah subjek penelitian. Pemeriksaan laboratorium dilakukan terhadap dua parameter yang diteliti yaitu kadar kreatinin serum dan BUN. Sementara itu, untuk parameter klirens kreatinin diperoleh dari perhitungan menggunakan rumus Cockcroft-Gault. Prosedur penelitian ini telah dikaji dan disetujui oleh Komisi Etik Fakultas Kedokteran Universitas Brawijaya Nomor 88/EC/KEPK-S1-FARM/03/2019.

Sampel penelitian

Berdasarkan perhitungan rumus besar sampel, jumlah pasien minimal yang diperlukan adalah 35. Pada penelitian ini diperoleh subjek sebanyak 37 pasien yang memenuhi kriteria inklusi dan eksklusi. Perhitungan rumus besar sampel yang digunakan dalam penelitian ini adalah sebagai berikut[10]:

$$n1 = n2 = \left[\frac{(Z\alpha + Z\beta)S}{X1 - X2}\right]^2$$

$$n1 = n2 = \left[\frac{(1{,}64 + 1{,}28)0{,}02}{-0{,}01}\right]^2$$

n1 = n2 = 34,11 ~ 35 orang

Keterangan: n1 = n2 = besar sampel minimal; Zα = deviat baku alfa untuk α sebesar 5% untuk hipotesis satu arah (untuk α = 0,05 adalah 1,64); Zβ = deviat baku beta untuk β sebesar 10% (untuk β = 0,10 adalah 1,28); S = simpang baku dari dua kali selisih nilai antar kelompok (S = 0,02); X1 = kadar kreatinin serum minggu pertama 0,88 mg/dL[11]; X2 = kadar kreatinin serum minggu kedua 0,89 mg/dL[11]; X1–X2 = 0,88-0,89 = -0,01

Kriteria inklusi penelitian yaitu laki-laki atau perempuan dewasa berusia > 26 tahun; pasien didiagnosis PJK dan tidak memiliki riwayat penyakit ginjal kronis; belum terdiagnosis secara klinis mengalami penyakit renovaskular dan penyakit ginjal kronis; PJK bersifat stabil; mendapat terapi aspirin minimal 4 minggu; rutin mengonsumsi aspirin dosis-rendah (80 mg/hari); tidak memiliki kontraindikasi terhadap aspirin; serta bersedia berpartisipasi dalam penelitian. Sementara itu, kriteria eksklusi meliputi pasien yang mengalami lupus nefritis dan sepsis; menggunakan senyawa bersifat nefrotoksik seperti antibiotik golongan aminoglikosida, obat kemoterapi, dan agen radiokontras; memiliki riwayat penyakit gastritis; memiliki riwayat alergi terhadap aspirin; serta menggunakan OAINS selain aspirin. Komorbid pasien yang tidak memungkinkan disingkirkan dari penelitian meliputi *hypertensive heart disease,* hipertensi, gagal jantung, diabetes melitus tipe 2, *Non-ST-Elevation Infark Miokard,* strok, dan osteoartritis.

Pengumpulan data, lokasi penelitian, dan waktu penelitian

Instrumen penelitian menggunakan data primer dan data sekunder. Data primer yang digunakan yaitu kadar kreatinin serum dan BUN. Pemeriksaan kadar kreatinin serum dan BUN tidak dilakukan secara rutin untuk pasien PJK di rumah sakit tempat dilakukannya penelitian (RSI UNISMA Kota Malang) sehingga peneliti melakukan pemeriksaan terhadap kedua parameter tersebut. Pengambilan sampel darah dilakukan di laboratorium RSI UNISMA Kota Malang terhadap pasien PJK sebanyak 2 kali yaitu bulan ke-1 dan ke-3 sejak dimulainya penelitian. Penelitian dilakukan pada bulan Maret-Juni 2019. Data sekunder merupakan data demografi pasien yang diambil dari rekam medis meliputi umur, jenis kelamin, riwayat penyakit, riwayat pengobatan, dan lama penggunaan obat. Data kadar kreatinin serum dan BUN tidak terdapat di dalam rekam medis pasien karena kedua parameter tersebut tidak diperiksa secara rutin untuk memantau fungsi ginjal pasien yang mendapat terapi aspirin jangka panjang.

Tabel I. Data Demografi

Parameter	Jumlah	Persentase (%)
Umur		
31-40 tahun	1	2,70
41-50 tahun	8	21,62
51-60 tahun	11	29,73
61-70 tahun	15	40,54
71-80 tahun	2	5,41
Total	**37**	**100**
Jenis Kelamin		
Laki-Laki	25	67,6
Perempuan	12	32,4
Total	**37**	**100**
Lama Penggunaan Aspirin		
1 bulan s.d < 6 bulan	21	56,8
6-12 bulan	8	21,6
> 12	8	21,6
Total	**37**	**100**

Analisis data

Data pasien yang telah diklasifikasi disajikan dalam bentuk persentase. Data numerik diolah dalam bentuk desimal dan disajikan dalam bentuk rerata ± simpangan baku (s.b). Selanjutnya, data-data tersebut ditampilkan dalam bentuk tabel.

Analisis penurunan fungsi ginjal dilakukan dengan membandingkan parameter-parameter terkait fungsi ginjal yaitu kreatinin serum, klirens kreatinin, dan BUN. Pemeriksaan dilakukan sebanyak dua kali yaitu pada bulan ke-1 dan ke-3. Sebelum dilakukan uji perbandingan, peneliti melakukan uji normalitas distribusi data dengan uji Shapiro-Wilk karena besar sampel ≤ 50 subjek. Uji t berpasangan dilakukan untuk mengetahui perbedaan hasil pengukuran kadar kreatinin serum, klirens kreatinin, dan BUN pada bulan ke-1 dan ke-3. Sementara itu, uji *One Way ANOVA* dilakukan untuk melihat pengaruh durasi pemakaian aspirin yang dibagi dalam 3 kelompok waktu terhadap kadar kreatinin serum, klirens kreatinin, dan BUN. Nilai $p < 0,05$ menunjukan hasil yang signifikan secara statistik.

HASIL DAN PEMBAHASAN

Terdapat 37 pasien yang bersedia menjadi subjek penelitian, terdiri dari 25 (67,6%) pasien laki-laki dan 12 (32,4%) pasien perempuan. Rata-rata umur pasien adalah 57,56 tahun. Lama penggunaan aspirin yang paling banyak adalah 1 bulan sampai dengan kurang dari 6 bulan. Data demografi pasien diuraikan pada Tabel I.

Aspirin dosis rendah merupakan terapi yang direkomendasikan untuk mencegah keparahan PJK. Dosis rendah yang digunakan untuk terapi antiagregasi platelet yaitu 75-325 mg/hari[12]. Pada penelitian ini dosis aspirin yang digunakan sebesar 80 mg/hari. Dari data demografi diperoleh subjek penelitian yang terbanyak adalah pasien dengan umur 61-70 tahun dengan rentang umur pasien secara keseluruhan adalah 39-75 tahun. Umur merupakan faktor risiko PJK sehingga dengan bertambahnya umur akan meningkatkan risiko terjadinya PJK. Semakin bertambah umur dapat meningkatkan kadar kolesterol total yang menyebabkan penumpukan kolesterol, meningkatkan risiko timbulnya plak yang menempel di dinding pembuluh

Tabel II. Perbandingan Kadar Kreatinin Serum, BUN, dan Klirens Kreatinin pada Bulan ke-1 dan Bulan ke-3

Kategori	N	Rerata ± simpangan baku		p
		Bulan Ke-1	Bulan Ke-3	
Kreatinin serum (mg/dL)	37	1,03 ± 0,27	1,03 ± 0,29	0,963
Klirens kreatinin (mL/menit)	37	73,16 ± 18,14	72,92 ± 19,76	0,929
BUN (mg/dL)	37	13,05 ± 4,10	14,65 ± 4,44	0,052

Uji t berpasangan; signifikan secara statistik jika $p < 0,05$

darah koroner, dan mengganggu aliran darah[13].

Mayoritas subjek dalam penelitian ini berjenis kelamin laki-laki karena laki-laki lebih berisiko mengalami PJK dibanding wanita. Salah satu kriteria inklusi dalam penelitian ini adalah pasien dengan PJK. Hal ini sesuai dengan hasil penelitian oleh Lansky *et al.*, (2012) yang menunjukkan bahwa laki-laki lebih berisiko mengalami kematian akibat PJK IMA (infarktus miokardia akut) dibanding wanita. Hal ini disebabkan oleh laki-laki memiliki bentuk lesi plak aterosklerosis yang mudah ruptur, volume inti nekrosis yang lebih banyak, densitas kalsium yang lebih banyak, serta jaringan fibrosa dan *fibrofatty* yang lebih banyak dibanding wanita[14]. Berdasarkan penelitian oleh Bots *et al.*, (2017) juga menunjukkan bahwa kematian PJK lebih tinggi pada laki-laki daripada perempuan sepanjang masa dewasa. Bots *et al.*, (2017) menjelaskan bahwa laki-laki umumnya berkembang penyakit kardiovaskular pada umur yang lebih muda dan memiliki kecenderungan berkembang lebih tinggi menjadi PJK dibandingkan perempuan[15]. Seluruh pasien dalam penelitian ini mendapat aspirin karena aspirin dosis-rendah (75-100 mg/hari) dapat dipertimbangkan untuk pencegahan primer penyakit kardiovaskular aterosklerosis[16]. Namun demikian, tidak semua pasien yang mengonsumsi aspirin dapat terbebas dari efek samping berupa nyeri lambung. Berdasarkan penelitan tentang karakteristik penderita dispepsia mengemukakan bahwa perempuan lebih mudah mengalami dispepsia karena faktor psikologis dan hormon seks[17]. Pasien yang mengalami dispepsia atau keluhan nyeri lambung tidak dapat diberi terapi antiagregasi platelet berupa aspirin. Oleh karena itu, pada penelitian ini pasien laki-laki lebih banyak daripada pasien perempuan karena pasien perempuan diberi terapi antiagregasi platelet selain aspirin.

Dalam penelitian ini, penilaian fungsi ginjal pada pasien PJK yang mendapat terapi aspirin 80 mg/hari menggunakan parameter kreatinin serum, BUN, dan klirens kreatinin. Didapatkan rerata kreatinin serum bulan ke-1 sebesar 1,03 ± 0,27 mg/dL dan bulan ke-3 sebesar 1,03 ± 0,29 mg/dL; rerata nilai klirens kreatinin bulan ke-1 sebesar 73,16 ± 18,14 mL/menit dan bulan ke-3 sebesar 72,92 ± 19,76 mL/menit; rerata kadar BUN bulan ke-1 sebesar 13,05 ± 4,10 mg/dL dan bulan ke-3 sebesar 14,65 ± 4,44 mg/dL. Kadar kreatinin serum, BUN, dan klirens kreatinin pada bulan ke-1 dan bulan ke-3 yang diuji dengan uji t berpasangan menunjukan tidak ada perbedaan rerata yang signifikan secara statistik ($p > 0,05$) (Tabel II).

Hasil perbandingan kadar kreatinin serum, BUN, dan klirens kreatinin pasien pengguna aspirin dosis-rendah dalam jangka panjang tidak menunjukan perbedaan rerata yang signifikan. Pada parameter fungsi ginjal yaitu rerata nilai kreatinin serum dan BUN terdapat kecenderungan meningkat dari bulan ke-1 ke bulan ke-3. Rentang nilai kreatinin serum pada bulan ke-1 yaitu 0,76-1,30 mg/dL sedangkan pada bulan ke-3 yaitu 0,74-1,32 mg/dL. Dari rentang nilai tersebut terlihat bahwa kadar kreatinin serum tertinggi bulan ke-1 dan bulan ke-3 masing-masing adalah 1,30 mg/dL dan 1,32 mg/dL. Hal ini

menunjukkan jika penggunaan aspirin dosis-rendah jangka panjang meningkatkan parameter kreatinin serum (nilai rujukan normal adalah 0,5-1,1 mg/dL untuk perempuan dan 0,6-1,2 mg/dL untuk laki-laki).

Sementara itu, untuk nilai klirens kreatinin dari bulan ke-1 hingga bulan ke-3 tampak mengalami sedikit penurunan yaitu 0,33%. Namun demikian, nilai klirens kreatinin dari hasil penelitian ini seperti ditunjukkan pada Tabel II termasuk rendah karena seperti diketahui bahwa rentang normal klirens kreatinin adalah 110-150 mL/menit (untuk laki-laki) dan 100-130 mL/menit (untuk perempuan)[18]. Penurunan klirens kreatinin dapat mengindikasikan adanya penurunan fungsi ginjal dalam mengekskresi produk-produk buangan dan toksin seperti urea, kreatinin, dan asam urat[19]. Berdasarkan klasifikasi tingkat penyakit ginjal kronis dari pedoman K/DOQI (*Kidney Disease Outcomes Quality Initiative of the National Kidney of the National Kidney Foundation*), hasil penelitian ini dengan nilai klirens kreatinin pada bulan ke-1 dan bulan ke-3 yang berada dalam rentang 60-90 mL/menit termasuk dalam penyakit ginjal kronis tingkat 2 yaitu kerusakan ginjal dengan penurunan laju filtrasi glomerulus ringan[20]. Parameter-parameter fungsi ginjal dalam penelitian ini menunjukkan adanya potensi penurunan fungsi ginjal pada pasien yang menggunakan aspirin dosis-rendah dalam jangka panjang. Selain itu, proses penuaan pada lansia juga dapat berkontribusi menurunkan fungsi ginjal[21].

Dalam praktik klinik, kadar kreatinin serum dan BUN digunakan untuk mengetahui fungsi ginjal. Kreatinin serum merupakan produk metabolik dari massa otot dan diproduksi secara konstan kemudian diekskresi melalui ginjal. Untuk itu, kreatinin serum dapat dijadikan sebagai penanda jika terjadi penurunan fungsi ginjal. Namun demikian, kreatinin serum dapat dipengaruhi oleh massa otot, umur, jenis kelamin, dan aktivitas sehari-hari sehingga memungkinkan terjadi peningkatan atau penurunan tergantung faktor yang mempengaruhinya. Pemeriksaan BUN juga dapat digunakan untuk mengidentifikasi adanya kelainan pada ginjal. Urea serum atau BUN meningkat pada saat klirens ginjal menurun. BUN juga dapat meningkat pada kondisi yang tidak ada keterkaitannya dengan ginjal seperti saat dehidrasi dan diet tinggi protein. Rasio dari kreatinin dan BUN sangat berguna untuk mengetahui kelainan pada ginjal. Selain itu, BUN akan meningkat pertama kali saat ginjal mengalami kelainan[19].

Selain kreatinin serum dan BUN, perhitungan klirens kreatinin juga terbukti dapat menjadi indikasi fungsi ginjal yang lebih baik daripada hanya melihat hasil pengukuran kreatinin serum karena perhitungan klirens kreatinin (rumus Cockcroft-Gault) menggunakan umur, tinggi badan, berat badan, jenis kelamin, dan nilai kreatinin serum[22]. Klirens kreatinin dapat dijadikan cerminan dari penilaian laju filtrasi glomerulus.

Berdasarkan data dari 37 pasien yang terlibat dalam penelitian ini, persentase lama penggunaan aspirin yang terbanyak adalah 1 bulan sampai kurang dari 6 bulan. Hasil uji *One Way ANOVA* terkait pengaruh lama penggunaan aspirin terhadap kadar kreatinin serum, BUN, dan klirens kreatinin menunjukan tidak terdapat perbedaan rerata yang signifikan (Tabel III). Hal ini menunjukkan jika pengaruh pemberian aspirin tidak dipengaruhi oleh lama penggunaan tetapi dapat dipengaruhi oleh faktor lain seperti besaran dosis yang diberikan[7,23]. Penelitian oleh Mahto (2017) menyebutkan bahwa pemberian aspirin dosis 100 mg/hari tidak menunjukkan adanya peningkatan yang signifikan terhadap kadar kreatinin serum dan urea. Akan tetapi, pemberian aspirin dosis 300 mg/hari menunjukan peningkatan yang signifikan pada kadar kreatinin serum dan urea[23]. Penelitian lain yang serupa menyebutkan bahwa pada pemberian aspirin dosis 300 mg/hari relatif menurunkan klirens kreatinin secara signifikan dibandingkan pemberian aspirin dosis 60 mg/hari[22]. Namun demikian,

Tabel III. Pengaruh Lama Penggunaan Aspirin terhadap Kadar Kreatinin Serum, BUN, dan Nilai Klirens Kreatinin

		N	Kreatinin Serum (mg/dL)		Klirens Kreatinin (mL/menit)		BUN (mg/dL)	
			Rerata ± s.b	p	Rerata ± s.b	p	Rerata ± s.b	p
Lama Penggunaan	1 bulan sampai < 6 bulan	21	1,00 ± 0,28	0,720	74,05 ± 15,62	0,882	12,43 ± 3,12	0,320
	6-12 bulan	8	1,01 ± 0,33		73,75 ± 22,37		12,75 ± 3,45	
	> 12 bulan	8	1,10 ± 0,20		70,25 ± 21,95		15,00 ± 6,41	

Uji *One Way ANOVA*; signifikan secara statistik jika p < 0,05
s.b: simpangan baku

jika fungsi ginjal dalam penelitian ini dilihat dari parameter klirens kreatinin terlihat bahwa pada semua kelompok lama penggunaan mengindikasikan adanya penurunan laju filtrasi glomerulus ringan dengan kecenderungan semakin lama penggunaan aspirin maka nilai klirens kreatinin juga semakin menurun yaitu 74,05 mL/menit (penggunaan 1 bulan sampai kurang dari 6 bulan) menjadi 73,75 mL/menit (penggunaan 6-12 bulan) kemudian menjadi 70,25 mL/menit (penggunaan lebih dari 12 bulan). Selain itu, pada parameter kreatinin serum juga menunjukkan kecenderungan meningkat yaitu 1,00 mg/dL pada durasi penggunaan aspirin 1 bulan sampai kurang dari 6 bulan kemudian meningkat menjadi 1,01 mg/dL pada durasi penggunaan aspirin 6-12 bulan dan meningkat lagi menjadi 1,10 mg/dL pada durasi penggunaan aspirin lebih dari 12 bulan. Demikian juga pada parameter BUN juga menunjukkan peningkatan selama durasi terapi aspirin mulai dari 12,43 mg/dL meningkat menjadi 12,75 mg/dL dan kembali meningkat menjadi 15,00 mg/dL.

KETERBATASAN PENELITIAN

Keterbatasan dalam penelitian ini adalah tidak banyak subjek penelitian dengan durasi penggunaan aspirin 80 mg/hari yang lebih dari dua tahun. Jumlah subjek penelitian dengan durasi penggunaan aspirin lebih dari etdua tahun hanya 3 pasien (8,11%).

KESIMPULAN

Berdasarkan penelitian yang telah dilakukan disimpulkan bahwa penggunaan aspirin dosis-rendah jangka panjang berpotensi menyebabkan penurunan fungsi ginjal dilihat dari adanya penurunan nilai klirens kreatinin serta peningkatan kreatinin serum dan BUN.

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JMPF Vol. 10 No. 3 : 195-203
ISSN-p : 2088-8139
ISSN-e : 2443-2946

The Effectiveness of Zoledronic Acid and Ibandronic Acid in Delaying Skeletal-Related Events in Multiple Myeloma in Indonesia

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Submitted: 18-11-2019 *Revised: 13-06-2020* *Accepted: 11-09-2020*

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ABSTRACT

Zoledronic acid and ibandronic acid are listed in the Indonesian national formulary to prevent skeletal-related events (SRE) in patients diagnosed with bone metastasis in multiple myeloma (MM), with limited evidence to compare their effectiveness. This study aimed to investigate the effectiveness and safety of zoledronic acid and ibandronic acid in delaying SRE. The method was the retrospective, with data obtained from the multicenter study for MM patients with bone metastasis (aged over 18 years), based on medical records between January 2016 and December 2018. Patients were assigned to zoledronic acid and ibandronic acid groups. The clinical outcome was the next SRE which consists of vertebral/bone fracture, spinal cord compression leading to the need for surgery or radiation, and adverse event (AE) due to 2 years of drugs usage. Result of this research was made up of a total of seventy (70) patients with 40 in the zoledronic acid group, and 30 in ibandronic acid. At median treatment duration of 8 months (range: 2 – 24 month), SRE incident in zoledronic acid and ibandronic acid were 20.0 % and 23.3 % respectively. Furthermore, their mean SRE free survival times were 21 months [95% confidence interval (CI) 19 - 23 months], and 19 months [95% CI, 16 – 22 months], respectively. Also, their time intervals were not significantly different (p>0.05). The osteonecrosis of the jaw (ONJ) was AE which occurred more in zoledronic acid than ibandronic acid. The conclusion was zoledronic acid tends to delay SRE time compared to ibandronic acid, although more ONJ occur.

Kata kunci: Multiple myeloma; zoledronic acid; ibandronic acid; SRE; safety

INTRODUCTION

Multiple myeloma (MM) is a haematology malignancy which often occurs with a global mortality rate of 1% compared to cancer incidence. According to the Asian Myeloma Network (AMN), its occurrence in Asia is not significantly different to the west. In Indonesia, its prevalence was the second largest incidence of blood cancer, with a median survival rate of 3 to 10 years [1,2]. Tadjoedin *et al.,* (2011) stated that the characteristics of MM patients in Indonesia were dominated by unemployed, Javanese, with high school education. Most patients had less than 30% plasma cells in their bone marrow, proteinuria, negative Bence Jones, and positive serum monoclonal gammopathy. Nearly 50% of patients had stage IIIA with melphalan/prednisone as the most widely used chemotherapy[3].

Metastasis in MM targets bone, therefore, 80% of patients experienced bone metastasis through an osteolytic process, osteoporosis, or fracture at diagnosis [4,5]. Patients with bone metastasis experience significant morbidity and mortality with a high risk of skeletal-related events (SRE) such as pathological fracture, spinal cord compression, thereby, leading to the need for radiotherapy and surgery [6,7].

Bisphosphonate is an essential therapy for the prevention of bone metastasis[8], and this is in addition to the intravenous form of ibandronic acid or zoledronic acid listed in the Indonesian National Formulary[9]. The choice of both drugs was still limited by the minimum head to head comparative research of the two drugs. Several systematic review and meta-analysis had discussed the medicines that were more potent for bone metastasis.

A review of Mhaskar *et al.,* (2010) on the effectiveness of zoledronic acid and ibandronic acid in MM patients showed that these therapies were capable of reducing pathological vertebral fractures, SRE, and pain, but not mortality[10]. Palmieri *et al.,* (2013) also gave the same results using a meta-analysis. In multiple myeloma, the SRE incidence rate was 1.43 for zoledronic acid and 2.49 for ibandronic acid, which means that zoledronic acid is associated with a lower incidence of SRE than ibandronic acid [5].

According to De Cock *et al.,* (2005), discontinuity of both acids use tends to occur due to adverse drug reactions (ADR) or complications. The potential problems need to be studied owing to costs with osteonecrosis of the jaw (ONJ) as an adverse event of using bisphosphonates[6]. A study of the ONJ incidence in zoledronic acid and ibandronic acid on a total of 780 patients stated that 81% had ONJ on zoledronic acid groups and 9% on ibandronic acid group, which was influenced by gender and cancer type[11]. A retrospective study of medical records showed that renal toxicity in MM patients significantly increased on zoledronic acid compared to ibandronic acid[12]

Research on their effectiveness has never been conducted in Indonesia. Therefore, this study aim at investigating the effectiveness of IV zoledronic acid and IV ibandronic acid as SRE prevention in MM patients to monitor and evaluate its usage. The study was also used in clinical pathways development, in documents that reflect standards and services of both doctors, nurses and other health teams where each intervention is given a systematic record and expected to improve the quality of home care in Indonesia.

METHODS

Study design and data collection:

This study was retrospective research, conducted at the national hospitals under Dr. Sardjito Yogyakarta and Dr. Kariadi Semarang. The two hospitals were chosen because the cancer therapy centers in both hospitals are national references for cancer therapy and research.Data was taken from medical records, and its collection was through a case report form (CRF) containing the patient's demographic and clinical characteristics, treatments, outcome, and adverse event (AE).

The inclusion criteria were adult patients above 18 years, diagnosed with symptomatic multiple myeloma that used zoledronic acid or ibandronic acid from January 2016 to December 2018. Patients with bone lesions or SRE in the axial skeletal survey were included as the baseline, while those with incomplete medical records were excluded.

The result of previous study were used to estimate the minimum sample size. Menssen *et al.,* (2002) stated that the proportion of SRE in the ibandronic acid group IV compared to placebo was 54.55% versus 52.53%.[13] The study of Aviles *et al.,* (2013) stated that the proportion of SRE in the zoledronic acid group compared to placebo groups was 14.57 % versus 24.20%.[14]

Minimum sample size was estimated using the formula[15]:

$$n1 = n2 = \frac{\{Z_{1-\frac{\alpha}{2}}\sqrt{2P(1-P)}+Z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\}^2}{(P_1-P_2)^2}$$

$Z\ 1\text{-}\alpha/2 = 1{,}96$

$Z\ 1\text{-}\beta = 0{,}84$; $P1 = 0{,}55$; $P2 = 0{,}15$

The number of samples for each group (zoledronic acid versus ibandronic acid) according to the formula was a minimum of 21 people. The charctheristics of the samples in the two groups were matched based on age, gender, stage of disease, treatment duration, baseline of skeletal, comorbidities and type of chemotherapy. The overall MM patients who used ibandronic acid in two hospitals was thirty (30) people were registered in medical record from 2016 – 2018, so that the characteristics of patients using zoledronic acid were adjusted to match the ibandronic group. Forty (40) patients using zoledronic acid was found with charactheristics that match with the ibandronic acid group and have complete medical record data. Sample

acquisition for each groups in this study was representative.

Measurement and definitions:

The outcome was SRE incidence, SRE free survival times and AE. The primary outcome was SRE incidence of and SRE free survival times of all baseline skeletal in total sample of each drug group. The secondary outcomes were SRE free survival times based on baseline skeletal and AE.

The SRE was defined as vertebral/ another bone fractures and spinal cord compression with the need for radiotherapy or surgery. The AE were defined as ONJ, renal disorders and flue like symptoms. The SRE was seen from the results of radiological examination and medical records of patients. The AE was seen from medical records. Clinical outcomes and time intervals were traced from the first use of the drug to the next SRE incident or a maximum of 2 years. Time to event was time to SRE that define as the time interval from the first use of the drug to the date of SRE occurred.

Statistical Analysis:

The analysis was descriptive, with the equal group allocation designed to allow the hypothesis test of the different effectiveness of zoledronic acid and ibandronic acid groups.

The baseline characteristics of patients were compared using Chi-square on the categorical variables and Mann Whitney test or t-test on the continuous variables. Furthermore, descriptive statistics were used to report the patients' characteristics and incidents of SRE and AE.

The SRE incidence was reported as a percentage of SRE. The percentage of SRE was the number of samples of each drug group that experienced SRE divided by the number of samples of each drug group multiplied by one hundred percent. SRE free survival times was estimated by the Kaplan Meier test. Estimation was done by entering data of time to event and percentage of SRE of each groups in Kapplan Meier program. Two-tailed alpha significance less than 0.05 level was used for the analyzes of the differences of SRE free survival times between the two groups. Sree free survival times were further estimated based on baseline of skeletal.

Adverse event (AE) was reported as a percentage of AE thet occured in zoledronic acid or ibandronic acid groups. The percentage of AE was the number of samples for each group of drugs that have AE divided by the number of samples for each group of drugs.

RESULTS AND DISCUSSION

Characteristics of patients:

Zoledronic acid and ibandronic acid are supportive therapies for MM; however, there is limited evidence in comparing these two drugs. This study was, therefore, conducted to determine their effectiveness using seventy (70) patients diagnosed with MM and bone metastasis. Thirty (30) patients used ibandronic acid. The thirty patients who used ibandronic acid were total users of ibandronic acid in both hospitals that include in the criteria with complete and accessible medical records. The characteristics of patients with zoledronic acid were adjusted to patients with ibandronic acid so that forty (40) patients were found in the zoledronic acid groups with characteristics that matched with ibandronic acid groups.

The research was only done with 70 patients because of the low MM incident in the two hospitals. The new case of MM in Indonesia was small. Globocan (2018) stated that the new cases were 2,717 cases a year. It was the 20th rank of cancer incident in Indonesia[16].

The characteristics are shown in Table I, with Forty (40) patients at the zoledronic acid groups and 30 patients in ibandronic acid groups. There was no significant difference based on age, gender, Durie-Salmon stage, the baseline of skeletal, comorbid and chemotherapy type. The median treatment duration in both groups was 8 months, with the age range between 28–80 years. Men were more than women, with stage 3 greater than stage 2. Bone fracture was the most common

Table I. Characteristics of patients

Character	Zoledronic Acid n=40	Ibandronic Acid N=30	p-value
Age, years (Median (range))	57,5(34 – 80)	58,5(28 – 80)	0.867
Male sex, n(%)	25(62.5)	21(70.0)	0.513
Durie-Salmon stage, n(%)			
2	4(10.0)	2(6.7)	0.622
3	36(90.0)	28(93.3)	0.622
Treatment duration, month (Median (range))	8(2 – 24)	8(2 – 15)	0.303
Baseline of skeletal, n(%)			
Bone lesion	19(47.5)	16(53.3)	0.629
Bone fracture	12(30.0)	6(20.0)	0.343
Spinal cord compression	6(15.0)	6(20.0)	0.583
Combination of SRE	3(7.5)	2(6.7)	0.893
Charlson Comorbidity Index (median (range))	2(0-7)	2(0-6)	0.095
Type of chemotherapy,n(%)			
Melphalan, prednisone	27(67.5)	14(46.7)	0.080
Melphalan, prednisone, thalidomide	6(15.0)	7(23.3)	0.375
Vincristine, doxorubicin, dexamethasone	5(12.5)	8(26.7)	0.131
Thalidomide	2(5.0)	1(3.3)	0.733

SRE, skeletal related event

Mann-Whitney test was used to calculate p-value of treatment duration and Charlson comorbidity indexs. T-test was used to calculate p value of age. Chi square test was used to calculated p-value of gender, Durie-Salmon stage, baseline skeletal and type of chemotherapy.

SRE. Furthermore, the most widely used chemotherapy was melphalan – prednisone combination.

Base on patients characteristic, the majority were men above 50 years, in stage 3 Durie-Salmon stage, using melphalan-prednisone. This research was consistent with previous research which stated the characteristics of MM patients in Indonesia were dominated by male above 50 years, in stage 3 and using melphalan-prednisone[3].

The median treatment duration of both drugs was 8 months, which was due to government-guaranteed funding for that duration. Patients usually stop using after eight months because they cannot afford to pay. However, the optimal duration of bisphosphate use was indeed debated due to ONJ incident. Several guidelines suggested its use every month for two (2) years under the disease progression, bone, toxicity, or other laboratory data[17].

Effectiveness:

The ratio of patients with next SRE in the zoledronic acid and ibandronic acid groups was 20.0% and 23.3%, respectively (Table II). Spinal cord compression and vertebral fracture/another bone fracture often occur in each group. According to Kapplan Meier, the estimated mean SRE-free survival times of zoledronic acid and ibandronic acid were 21 months [95% confidence interval (CI), 19 - 23 months], and 19 months [95% CI, 16 - 22 months] respectively. Zoledronic acid tends to delay the incident by two months later than ibandronic acid with no significant time to the difference (p-value = 0.372 (> 0.05), figure 1).

The SRE-free survival time was further analyzed based on skeletal condition.

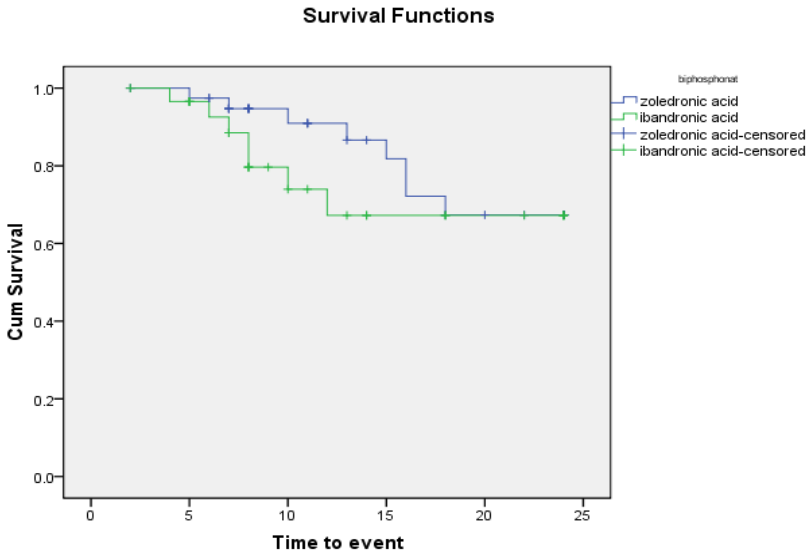

Figure 1. Kapplan Meier estimated SRE free survival time zoledronic acid versus ibandronic acid of all baseline skeletal

Table II. Incidence of SRE in patients subgroups by zoledronic acid or ibandronic acid treatments

Type of SRE	Zoledronic acid (n=40)	Ibandronic acid (n=30)
Vertebral fracture/ another bone fracture, n(%)	3(7.5)	2(6.6)
Need of surgery to bone,n(%)	0(0.0)	1(3.3)
Spinal cord compression,n(%)	5(12.5)	3(9.9)
Combination of SRE,n(%)	0(0.0)	1(3.3)
Total, n(%)	8(20.0)	7(23.3)

SRE, skeletal related event

In patients with bone lesions in the baseline, the mean SRE-free survival times in zoledronic acid and ibandronic acid were 21 months [95% CI, 18 – 24 months] and 18 months [95% CI, 14 – 23 months] respectively (figure 2). While those with SRE in the baseline, it was 20 months [95%CI, 18 – 23 months] and 20 months [95%CI, 15 – 24 months] (figure 3).

In this study, zoledronic acid reduced the risk of SRE 16.5% compared to ibandronic acid in MM patients with bone metastasis. Moreover, zoledronic acid groups have a longer time to SRE than ibandronic acid groups (21 and 19 months). Statistical analysis showed no significant difference between both groups in delaying time to SRE; however, the data showed the benefits of zoledronic acid, which was felt by patients. It was in accordance with the systematic review of Palmieri *et al.,* (2013) which stated that IV zoledronic acid (4 mg every 3 – 4 weeks) was associated with the lowest SRE incidence rate (1.43) compared with the comparative rates being 2.49 for IV ibandronic acid (6 mg every 3 – 4 weeks)[5].

Safety:

The most-reported AE was osteonecrosis of the jaw (ONJ) (Table III), which was more common in the zoledronic acid groups. The flue like symptoms and renal disorders were similar in both groups. However, ONJ was more common in the use of zoledronic acid than ibandronic acid. The

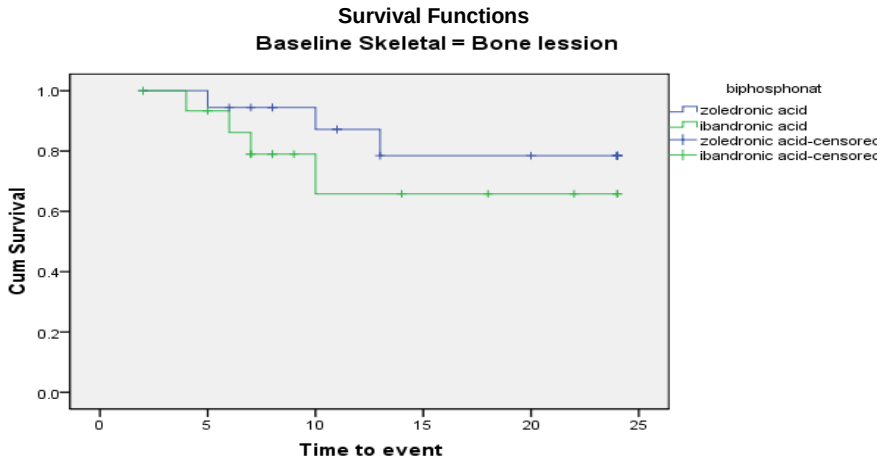

Figure 2. Kapplan Meier estimated SRE-free survival time of zoledronic acid versus ibandronic acid of patients with bone lesions as baseline skeletal

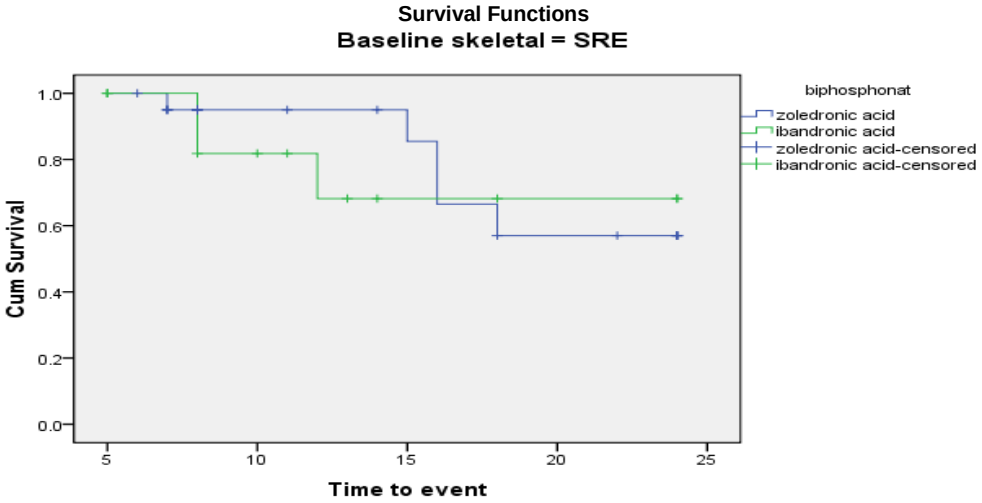

Figure 3. Kapplan Meier estimated SRE-free survival time of zoledronic acid versus ibandronic acid in patients with SRE as baseline skeletal

Table III. Adverse event in patients sub-groups by zoledronic acid or ibandronic acid

Type of Adverse Event	Zoledronic acid n=40	Ibandronic acid n=30
ONJ, n(%)	5 (12.5)	1(3.3)
Renal disorders, n(%)	1(2.5)	2(6.7)
Flue like symptoms, n(%)	1(2.5)	2(6.6)
Total, n(%)	7(17,5)	5(16,67)

ONJ, Osteonecrosis of the jaw

result was in concordance with the study of Gabbert *et al.,* (2014) which reported a total of 780 patients, with 81% experiencing ONJ during the zoledronic acid treatment and 9% during ibandronic acid[11].

Many cancer guidelines stated that ONJ is a significant clinical problem associated with long-term use of bisphosphonates. Its frequency is 1-2% of patients each year on monthly intravenous bisphosphonate therapy,

and this risk was reduced by the use of daily oral or intravenous administration with a 3-month schedule. Patients were advised to undergo dental examinations before the administration of bisphosphonate therapy to avoid the incidence of invasive teeth. However, when surgery or extraction of the jaw is unavoidable, prophylactic antibiotics need to be administered. Bisphosphonates need to be stopped until complete healing unless the patient was experiencing symptomatic bone[18].

AE associated with renal disorders was creatinine which increased and was reported in both acid groups. However, Weide *et al.*, 2010 study, was contrary to the previous retrospective results which stated that zoledronic acid significantly increased the risk and incidence of renal impairment compared to ibandronic acid[12].

The research proved that the choice of bisphosphonate therapy must adjusted to the safety of both drugs. Ibandronic acid should be used in MM patients with comorbid kidney disorders or having AE with kidney disorders when using zoledronic acid. Menssen *et al.*, (2002) reported that AE which occurred in ibandronic acid was only hypocalcemia[13]. These results were supported by the study of Terpos *et al.*, (2003) which reported the only incidence of hypocalcemia in ibandronic acid compared to pamidronate (0% versus 9%)[19]. While some RCTs reported renal toxicity in the use of zoledronic acid compared to placebo or other bisphosphonates. The RCTs stated thaht zoledronic acid caused more incident of renal toxicity compared to placebo[20–22].

Flue like symptoms was reported in both groups. The result was supported by some guidelines that stated intravenous use of bisphosphonate compounds was generally associated with acute phase responses (fever and flu-like symptoms), bone/joint pain, less common side effects such as kidney failure, ocular inflammation and atrial fibrillation[18]. However, the results of the study were not in accordance with those of a systematic review which stated that the symptoms of influenza and the fever incidence of ibandronic acid were slightly lower than zoledronic acid[23].

Overall, the results of the study stated that zoledronic acid could delay the incidences of SRE compared to ibandronic acid in MM patient with bone metastasis with a higher occurrence of ONJ. However, this study still had limitations in terms of patient number and its retrospective which led to lack of controlled comparisons such as RCT, drugs side effect, and the decision on initiation/ continuation of the treatment based on clinical practice preferences of individual physicians.

CONCLUSION

Zoledronic acid tends to delay time to SRE compared to ibandronic acid, with the occurrence of more ONJ. Periodic dental examinations and dental care were recommended during use of both drugs. The renal examination must also be done monthly. The use of both drug must be consider the nephrotoxic potential of the drug. Whenever there were evidence of renal insufficiency, the other drugs with less evidence of renal nephrotoxic must be used.

ACKNOWLEDGEMENTS

This research was received by the Ethics Commission of the Faculty of Medicine, Gadjah Mada University, Yogyakarta, with license number KEPK/FK/0852/EC/2018, as well as that of Kariadi Hospital Semarang (No.034/EC/KEPK-RSDK-2018). We thank all those who participated in this research.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

FINANCIAL SUPPORT

The research is a part of pharmacoeconomics study supported by the Indonesian Health Ministry Scholarship.

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JMPF Vol. 10 No. 3 : 204-219
ISSN-p : 2088-8139
ISSN-e : 2443-2946

The Effect of Based Services Medication Therapy Management on Treatment Adherence and Quality of Life of Diabetes Mellitus Patients

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder that is characterized by hyperglycemia. Diabetes mellitus need appropriate therapeutic management, because it can cause complications. On of the services that can do to improve diabetes control is Medication Therapy Management (MTM). MTM is a new service that will help pharmacist to improve patient adherence and quality of life. This study aims to determine the effect of based services MTM on treatment adherence and quality of life in patients with diabetes mellitus. This study was an experimental study using a quasi-experimental with one group pretest and posttest design which was conducted in Tegalrejo, Jetis and Gedontengen Health Center Yogyakarta City. Variables measured were medication adherence using the Morisky-Green Levine Medication Adherence Scale (MGLS) questionnaire and quality of life using Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ) before and after MTM services. The effect of MTM on medication adherence was analyzed using Wilcoxon test and the effect of MTM on quality of life using Paired T-Test. The patients participate in this study were 20 people, with average score of adherences before application of MTM was 2.20±0.410 to 1.80±0.616 after the application of MTM (P=0.005) and the average of the patient's quality of life was 73.82±7.918, increased to 76.42±5,623 after MTM service (P=0.033). Statistically mean, there is a difference in adherence and quality of life before and after MTM services. Therefore, it can be concluded that MTM-based services performed by pharmacists have a significant effect on improving medication adherence and quality of life for DM patients. Moreover, it can facilitate monitoring patient therapy, and identification of problems related to the treatment.
Keywords: Diabetes mellitus; adherence; quality of life; medication therapy management; MTM

INTRODUCTION

Chronic disease is a condition that contributes greatly to health, including the patient's clinical, humanistic, and even economic conditions. One of the chronic diseases that receive special attention and must be managed properly is diabetes mellitus (DM)[1]. It's due to the fact that diabetes has impacts on the patient's well-being, productivity and quality of life[2]. The prevalence of diabetes all over the world continues to increase. In 2000, the prevalence of DM for all age groups reached 2.8% and is predicted to increase to 4.4% in 2030[3]. According to the Riskesdas 2018 data, in Indonesia, there was an increase in the prevalence of DM based on doctors' diagnosis at ≥15 years of age by 2% from the previous prevalence of DM in 2013, where DKI Jakarta Province had the highest DM prevalence of 3.4% and followed by the Special Region of Yogyakarta (DIY) with 3.1% in 2018[4]. Yogyakarta's health profile shows that DM is included in the top 10 non-communicable diseases with the number of cases and groupings of DM disease as many as 11,736 cases of non-classified DM (DM YTT) and 12,019 cases of insulin-independent diabetes in 2018[5]. Improving DM disease control can be accomplished with regular monitoring and consistent follow-up related to lifestyle modifications, regular blood glucose monitoring and medication adherence.[6]. However, ensuring the adherence to therapy regimens is one of the main challenges in achieving the desired therapeutic goals in DM patients, as DM is a chronic disease that requires various patient-centered collaborative care models to improve the treatment behavior in DM patients.

One of the feasible services is the Medication Therapy Management (MTM)

service. MTM is a new service provided by health care providers, including pharmacists, to ensure the best therapy results for patients. The objectives of the MTM service are to ensure that the drugs prescribed to patients are consumed appropriately, optimize patients' understanding of drug use, improve patient compliance with prescribed drug therapy, and reduce the risk of drug-related adverse events in order to improve the patient's quality of life.[7]. MTM includes five main elements, i.e. medication therapy review (MTR), personal medication record (PMR), medication-related action plan (MAP), intervention, and follow up[8]. These elements of MTM are expected to enhance the collaboration and communication between pharmacists, doctors and other health care professionals in caring for patients, as well as optimizing drug use for better results.[8]. Thus, the compliance and good quality of life are achieved for patients, particularly DM patients. Several studies have shown that improvements in the clinical outcome of diabetic patients are achieved through the provision of MTM services by pharmacists. Viswanathan *et al.*,[9] conducted a review of several studies with Cochrane data sources and International Pharmaceutical Abstracts related to the effectiveness of MTM service interventions provided to outpatients with chronic conditions, and the results showed that MTM improved appropriate drug prescribing, use of appropriate drugs, medication adherence and patient's quality of life[9]. Research conducted by Erku *et al.*,[10] showed that there was an increase in the compliance of patients who received MTM services by pharmacists[10]. In Indonesia, research related to MTM services has not been widely carried out, but research related to services carried out by pharmacists such as providing education, counseling, or booklets on drug use has been widely carried out and has a good impact on patient treatment.[11]. Presetiawati *et al.*,[11] and Septiar and Utami[12] state that counseling by pharmacists increased the adherence and quality of life for DM type 2 patients[11,12].

In Indonesia, the MTM service has been proclaimed by the government alongside with the Social Insurance Administration Organization (BPJS) since 2017/2018 and has been implemented in several community health centers (*puskesmas*) in Yogyakarta City. One of them is the public health center, where the research is conducted, that provides MTM services to chronic disease patients, in this case the Referral Patient (PRB). The MTM service uses a sheet containing MTM elements listed by the BPJS, used by the patients every time they visit a public health center. Based on the existing MTM form, problems in filling the form persist due to the large number of sheets that must be filled in by health workers, especially pharmacists. Therefore, it is necessary to simplify the MTM form to facilitate the implementation of MTM in public health centers. Accordingly, this study aims to determine the effect of MTM-based services (simplified MTM) applied by pharmacists on medication adherence and DM patients' quality of life at Yogyakarta city health centers.

METHOD

This research is an experimental research using a quasi-experimental one group design with pretest and post-test design which was carried out at the Yogyakarta City's Puskesmas Tegalrejo, Jentis and Gedongtengen in March-April 2020. The variables measured in this study were medication adherence and DM patients' quality of life before (Pre-MTM) and after (Post-MTM) receiving MTM-based services. The intervention carried out in this study was in the form of MTM-based services provided by pharmacists to patients. The MTM services provided were in the form of implementing the MTM elements; 1) Assessment, i.e. the collection of information related to patient treatment and problems related to patient treatment (Element of Medication Therapy Review) and documentation of therapy received by patients (Element of Personal Medication Record); 2) Education and counseling, i.e. process of developing actions to achieve therapy goals by providing

information related to the disease and use of DM drugs to patients based on leaflet material (Elements of Medication Therapy Review). Meanwhile, counseling is a consultative service by pharmacists regarding drug use and/or patient treatment problems (Elements of Medication Related Action Plan); 3) Drug monitoring, i.e. follow-up visit service provided by a pharmacist according to the patient's needs (Element of follow up) and providing interventions in case of treatment-related problems, which is documented in the pharmacist documentation book. The measurements of Post-MTM conditions are carried out after 30 days after the MTM administration. This research has obtained permission from the Health Research Ethics Commission of the Faculty of Medicine, Universitas Gadjah Mada with No: KE/FK/0710/EC/2019.

Data Collection

Sample collection was conducted through consecutive sampling i.e. samples which fulfilled the inclusive requirements i.e. the patients with type 2 DM age ≥ 18 years old, patients who undergo regular check-up at least 1 month before the research, Patients who are willing to be the respondents, and having the promissory letter signed (informed consent), until the number of samples are complete. Furthermore, for patients who could not communicate properly or did not cooperate, patients whose jobs are the health worker, and patients who did not participate in this research till the end are not included in this research. Compliance data is obtained from the Morisky-Green Levine Medication Adherence Scale (MGLS) questionnaire. MGLS questionnaire was formerly developed by Morisky *et al.,* to assess medication compliance toward anti-hypertensive regimen in the USA[13]. Moreover, the MGLS questionnaire also has been used to assess medication compliance within the study of other chronic illnesses such as diabetes[14,15], cardiovascular diseases[16], asthma[17], and cancer[18]. Quality of life assessment is using Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ). The DQLCTQ questionnaire used for assessing a patient's quality of life in this research is referred to previous research conducted by Hartati in 2003, in RSUP Dr. Sardjito whose validity test had been performed towards DM patients[19].

The compliance and quality of life questionnaires were given to the patients before receiving MTM based service as Pre-MTM data. Furthermore, the DM patients would receive MTM based service from the pharmacist and upon receiving MTM based service in the next month according to regular checkup schedules which underwent in April 2020, the patients would be given the compliance and quality of life questionnaires once more as Post-MTM data.

Intervention

This research is an experimental one with intervention given in the form of MTM based service from the pharmacists to the DM patients. MTM based service that performed in this research was not a pure MTM instead it was a simplified form of MTM service according to the form made by BPJS as well as the elaboration of the existing theory of MTM. Therefore, it adapted according to the pharmacist's input and the needs of the community health center where the research took place. The form of implementation of MTM based service from the pharmacists including assessment, counseling, and education, as well as intervention/follow up toward DM patients delivered through medication record book. The medication record book consists of two books, the one which brought and kept by patients called "Smart and Control of DM medicine book" should be brought in every check-up contains MTR elements (demography, patient history, complaints, and physical examination), PMR (patient's medication-taking monitoring) and leaflet compiled by the research team and kept by the pharmacist "Documentation Book (Personal Medication Record)" contains the pharmacist's record about patient's medication and the intervention that had been performed. The objection of making this

medication record book is simplifying and helping the pharmacist to implement MTM service in the community health center. The selection of the community health center of Tegalrejo, Jetis, and Gedongtengen as the place of research is based on the readiness of the health centers and the willingness of the pharmacist especially for implementing MTM based service, in this case the simplified form of MTM by the research team as well as the DM patient's prevalence in the health centers.

MTM based service delivered by the pharmacists of the health center to patients at the time of the patient's monthly check-up with implementation period of the MTM based service is one month. Before MTM-based services were applied to DM patients, pharmacists in each health center were provided training regarding the implementation of MTM-based services and Standard Operating Procedures for MTM-based services in the form of FGD. The pharmacists that participated in this research were three persons, who would deliver MTM based service to the patients and be helped by the researcher after the patients filled the Pre-MTM data in March 2020.

MTM based service was started with the assessment stage which was information gathering related to the patients' history, complaints, the recent medication the taking that was recorded on the assessment page of the smart book of medication control by the researcher. The result of physical/laboratory examination, allergy, comorbidity diseases, and herbal remedy consumption was recorded on monthly check-ups by the patients while the first recorded assisted by the researcher. Whereas the self-examination page contains the results of blood pressure and blood sugar measurement done by patients themselves and patient's medication schedule for a month on the therapy monitoring was recorded by patients. The second stage was initial education delivered by the researchers and for the next education were delivered by the pharmacists in the community health center while the patients receive their drugs. The educational material provided is based on the leaflet material, namely related to DM, the benefits of taking medication, how to use DM drugs, how to control blood sugar and the signs of side effects in using drugs in the smart book of medication control. Furthermore, when the drug was delivered, the pharmacist would reconfirm the information on the assessment page and the monthly check-up page written in the DM patient's smart book of medication control, identify drug problems and re-educate the patients regarding the disease and the medication of DM patients. Counseling would be given after that related to the patients' medication problems and/or complained of trouble from patients regarding the disease or current medication. The last stage was observation/follow-up done by the pharmacists toward patients' medication and making intervention if there any problem related to medication recorded by the pharmacists on the pharmacist's record book. Implementation period of MTM service was one month.

Assessing Tools

Compliance Degree

The questionnaire used for assessing the DM patients' compliance degree in this research is Morisky-Green Levine Medication Adherence Scale (MGLS). MGLS questionnaire is a free-access instrument for assessing compliance containing 4 questions items[20], the answers for the items either "Yes" or "No", with the MGLS score result ranging from 0 to 4. Compliance data obtained is in the form of the ratio, based on the lowest score (0) signifies the high compliance, score 1-2 signifies moderate compliance, and score 3-4 signifies low compliance. This MGLS questionnaire has been translated in Language Center of Faculty of Cultural Science, Gadjah Mada University.

According to previous research conducted by Wang et. Al[13] the MGLS questionnaire had been validated and obtained the score of Cronbach's alpha = 0.62, a proof that showed Morisky-Green Levine is a specific questionnaire for the compliance assessment[13]. Validation toward MGLS

questionnaire in this research also has been performed through face validity method which tested 10 DM patients in the community health center of Yogyakarta city, the location of this research. According to the result of MGLS questionnaire's face validity, > 80% respondents understood the question items and the language style. Moreover, there are no ambiguity in the questions of the MGLS questionnaire, the questions items are clear, respondents could answer the questions, the questions have been in a good order (90%), and the words pronunciation are correct, as well as the interview period is short. From these results, it is expected that the MGLS questionnaire can be used to assess the patients' compliance degree.

Quality of Life

Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ) is a questionnaire used to assess quality of life related to the wellness of DM patients. DQLCTQ covers 57 items consisting of eight domains. Complete DQLCTQ questionnaire data is scored, with a total range from 0 up to 100. Score 0 signifies the lowest quality of patients' lives and 100 signifies the highest. Higher score signifies better wellness status.

The DQLCTQ questionnaire used for assessing patient's quality of life in this research refers to a previous research conducted by Hartati in 2003, in RSUP Dr. Sardjito, Yogyakarta toward Type 2 DM patients, with number of sample as much as 35 type 2 diabetes mellitus patients in RSUP dr. Sardjito which was conducted in January until March 2003. Validity and reliability tests including response, inter-item correlation, total item correlation, and internal consistency, as well as item status determination. The analysis results of complete item of the internal consistency value of all items, obtained valid and reliable results with a value of α = 0.82 (> 0.7) based on the result, the DQLCTQ questionnaire can be used to assess type 2 DM patients' the quality of life[21].

Statistical Analysis

The effect of MTM based service on medication compliance is analyzed with Wilcoxon test, while MTM effect on the quality of life analyzed with Paired T-Test, and for the characteristic effect on compliance and quality of life is using Ancova test with significance rate that can be used is $P < 0.05$. Patients' characteristics are depicted descriptively.

RESULTS AND DISCUSSION

Patients Characteristics

This research was conducted in three community health centers that is Puskesmas Tegalrejo, Gedongtengen, and Jetis. The subject of Initial research were 38 DM patients, however, the ones who participated in and met the inclusive requirements for this research fully (March-April 2020) were only 20 patients. Therefore, the analyzed total sample in this research was 20 DM patients. The depiction of DM patients' characteristics in this research could be seen in Table I.

According to the characteristics data, this research was dominated by females as many as 15 people (75%) and male as many as 5 persons (25%), with the most age group is 55-64 years old and as many as 8 people (40%). Sinuraya et. al,[22], in his research was also shown that the highest percentage of DM patients was female for about > 70%[22]. Moreover, several other pieces of research also showed the DM patients prevalence toward females was much more than the male patients[23–25]. Generally, the increased risk of DM disease is caused by lifestyle changes that lead to reduced physical activity and increased obesity[6]. This potentially more likely affects women for physically women are less active than men, with proportion as much as 27% for women and 20% for men who are categorized as physically inactive and represents a greater chance of increasing body mass index[26]. Furthermore, hormonal changes in women are much more than men especially related to premenstrual syndrome and post-menopause. Mauvais-Jarvis *et al.*,[27], suggest that there are changes to blood sugar homeostasis in the

Table I. Characteristics of A Diabetes Mellitus Patient

Characteristics	Number of subjects (N=20)	Percentage (%)
Gender		
Male	5	25
Female	15	75
Age		
< 45 years	4	20
45-54 years	6	30
55-64 years	8	40
65-74 years	2	10
Last education		
Elementary School	5	25
Junior High School	5	25
Senior High School	6	30
Diploma/Bachelor Degree	4	20
Occupation		
Employed	8	40
Unemployed	12	60
Marital Status		
Married	16	80
Widow	3	15
Widower	1	5
Duration of DM (duration of disease)		
< 1 years	4	20
1-5 years	6	30
6-10 years	6	30
≥ 10 years	4	20
Comorbidity disease		
With comorbids		
Hypertension	6	30
Without comorbids	14	70

bodies of women who have experienced menopause[27]. The decreased ability to control blood sugar is related to decreased levels of estrogen in the body[28]. The age of the respondents is dominated by the 55-64 years age group, categorized as the elderly group. Similar to research by Wild *et al.*,[3], diabetics are in the 40-64 years age range, especially in the developing countries[3]. In that age range, the function of organs decreases including the pancreas' function which causes insulin production starts to decline and along with the lifestyle that begins to be less maintained.

The characteristics of patients without comorbids were 14 people (70%) and patients with comorbid hypertension were 6 people (30%). The result of this study is in line with the research conducted by Katadi *et al.*,[24], Rokhman *et al.*,[23], that shows a number of DM patients with comorbid hypertension were found. The frequency of patients having diabetes for 1-5 years and 6-10 years has the same number of respondents, 6 people each (30%). The last educational background of the respondents are 6 people (30%) graduated from Senior High School, and the others

Table II. The Effects of MTM-Based Services on Treatment Adherence to Diabetes Mellitus Patients

Treatment	Compliance Degree			Average Compliance Score±SD	Deviation ± SD	P Score
	High N (%)	Average N (%)	Low N (%)			
Pre MTM	0	16 (80)	4 (20)	2.20 ± 0.410	-0.4 ± 0.50	0.005*
Post MTM	6 (30)	12 (60)	2 (10)	1.80 ± 0.616		

Note: *level of confidence 5% (P <0.05); Wilcoxon Analysis

graduated from Elementary School and Junior High School, 5 people each (25%). People's educational background influences the behavior and their awareness of health. DM patients with lesser education tend not to recognize the symptoms of DM[29]. According to the employment status, 12 people (60%) are unemployed patients, while 8 people (40%) worked. The unemployed group in this study was dominated by housewives. The majority of respondents, 16 people (80%), are married or have partners.

The Effect of MTM-Based Services on DM Patient's Compliance

This study was conducted to determine whether MTM-based services affect the adherence and quality of life of DM patients before and after conducted by pharmacists. MTM-based services are expected to increase medication adherence, and therefore a patient's quality of life is achieved with good results. The effect of MTM-based services on treatment adherence to DM patients in this study are shown in Table II. Assessment of medication adherence used the MGLS questionnaire, where the level of patient adherence was grouped into three categories: high adherence, moderate adherence and low adherence.

Based on the results in Table II, the increase of compliance is seen from the frequency obtained in each compliance category. Before the application of MTM, there were no patients who had a high level of adherence, and after the application of MTM there were 6 patients (30%) with high levels of adherence. Patients with the moderate adherence before MTM are 16 people (80%) and decreased to 12 people (60%) after MTM, while patients with low adherence are 4 people (20%) and decreased to 2 people (10%). The average score of patient adherence in this study was 2.20 ± 0.410 before MTM-based services, and 1.80 ± 0.616 after MTM-based services. According to the results, the compliance score decreased with a deviation score of -0.4 ± 0.50. Based on the measurement of adherence using MGLS, the lower the score obtained (score 3-4 for low adherence, 1-2 for moderate adherence, 0 for high adherence), the better the level of compliance. This shows that the treatment compliance of DM patients increased after receiving MTM-based services with a significance value obtained, P = 0.005 (P <0.05). From this statistical significance value, the MTM service provided by pharmacists affects the increase of DM patient compliance. Research conducted by Erku *et al.*,[10], revealed that the compliance of patients increased after receiving MTM services by pharmacists. The group of patients who were given MTM services had adherence from 9.2% to 61% after receiving MTM services[10].

In addition, the study conducted by Bindu Murali *et al.*,[2], obtained similar results, in which there was a significant increase after implementing MTM services (P = <0.05), initially 37.5% of the number of patients in the study who had high adherence and increased to 59.5% after being given MTM service and patients with low adherence decreased from 35.5% to 15.3%. Ndefo *et al.*,[30], also reported similar results, in which the average score of treatment adherence increased from 28.33 (94.4%) to 29.22 (97.4%). The MTM conducted

Table III. The Effects of Patient's Characteristics to the Compliance Score Change in DM Patient Treatment

Characteristics	Amount (N)	Compliance Score Change (Δ)	P Score
Gender			
Male	5	-1.00	0.670
Female	15	-0.40	
Age			
< 45 years	4	-1.00	0.431
45-54 years	6	-0.50	
55-64 years	8	-0.38	
65-74 years	2	-0.50	
Last education			
Elementary School	5	-0.60	0.173
Junior High School	5	-0.80	
Senior High School	6	-0.33	
Diploma/Bachelor Degree	4	-0.50	
Occupation			
Employed	8	-1.13	0.516
Unemployed	12	-0.17	
Duration of DM (duration of disease)			
< 1 years	4	-0.75	0.605
1-5 years	6	-0.50	
6-10 years	6	-0.17	
≥ 10 years	4	-1.00	
Comorbidity disease			
With comorbids	6	-0.50	0.977
Without comorbids	14	-0.57	

Note: *The analysis used Ancova Test; level of confidence 5% (P <0.05)

by pharmacists as part of the healthcare team led to a significant improvement in medication adherence[30].

The diabetes management program administered by pharmacists to patients also affects the improvement of patient's medication adherence in several previous studies. One of the studies is conducted by Manju *et al.*,[31], who attempted to find out whether the intervention given by pharmacists could improve treatment adherence to DM patients, measured before (Pretest) and after (Posttest) intervention. The interventions were education, counseling related to disease and medication as well as providing a chart of medication reminders that were asked to be brought to the next visit. Based on the measurement results, the poor adherence decreased from 48.2% to 26.1%, moderate adherence increased from 32.1% to 39.1% and high adherence increased from 19.7% to 34.9% with significance value of P = 0.000 (<0.05) which indicates that the treatment adherence of DM patients increased significantly after pharmacist intervention[31]. Research conducted by Shareef and Fernandes[32], and Butt *et al.*,[33], also showed similar results, in which pharmacist intervention through education, counseling, and monitoring related to disease and DM therapy possess a significant effect in improving treatment adherence to DM patients. Various studies related to the intervention conducted by pharmacists show a good effect on patient

medication adherence, which has the same result in this study that shows the effect of MTM services in increasing DM patient compliance. Research conducted by Bindu Murali *et al.*,[2], also shows that in addition to providing education and counseling, PMR, MAP, the diabetes calendars and/or leaflets provided as part of the MTM service program are effective in increasing the adherence of patient treatment.

The study shows that the level of patient adherence before being given MTM service by pharmacists, in which the level of patient adherence is moderate and low adherence, is lower than after MTM service. There are a number of factors that cause differences in treatment adherence in DM patients, one of which is patient's characteristics. Based on the data in Table III, without MTM-based service interventions (Pre and Post MTM), there is no difference in each group of gender characteristics on treatment adherence, with a significance value obtained of P = 0.670. Thus, gender characteristics do not affect changes in DM patient compliance scores. This study is similar to the one conducted by Rasdianah *et al.*,[34], which shows that there is no difference in adherence levels between men and women statistically. However, based on the percentage of adherence, female patients have better treatment adherence than male patients. Male DM patients have a greater tendency to forget in taking medication than their female partners (OR = 2.5, p <0.05)[35].

Patient's characteristics based on age in this study also shows that without MTM-based service interventions (Pre- and Post-MTM), each group of age characteristics has no effect on treatment adherence, with a significance value obtained P = 0.431, or there is no effect of age characteristics towards changes in DM patient compliance scores. This result is the same with the study by Rasdianah *et al.*,[34], which shows that age has no effect on medication adherence. However, other studies reveal different results in which age affects a person's adherence. Nanda *et al.*,[36], stated that the level of adherence decreases with age because at an older age the patient's memory decreases so that they tend to forget to take medication.

Bindu Murali *et al.*,[2], also revealed that there was a significant decrease in the level of adherence with increasing age (P = <0.05). Research conducted by Shams and Barakat[37], also states that adherence of DM patients is lower in the elderly, this is because of the awareness towards the importance of therapy that decreases and patient's forgetful memory which also affects elderly patient's compliance. In contrast to several previous studies, the one conducted by Kubais *et al.*,[38], shows that patients aged between 36-50 years showed the highest adherence while the 20-35 year age group showed low adherence to treatment. In this case, age can influence the treatment adherence of a person.

Based on the level of education, it shows that without the effect of MTM-based service interventions (Pre and Post MTM) there is no difference in each group of characteristics of the level of education on treatment adherence, with a significance value obtained, P = 0.173, which means there is no influence to changes in DM patient compliance scores. This result is different from the previous studies, patients with low educational status also had low adherence to treatment (p <0.05).[2]. The educational level of a person can influence adherence because educated patients are more aware of the long-term consequences and complications of diabetes, as well as the need for proper blood sugar control.[37].

Based on the job characteristics on this study, it shows that without the effect of MTM-based service interventions (Pre- and Post-MTM) there is no difference in each group of job characteristics on treatment adherence, with a significance value obtained P = 0.516, which means there is no characteristic effect work towards changes in DM patient compliance scores. These results are different from the studies conducted by Ainni in 2017 which showed the influences of work on patient treatment adherence[39].

The duration of disease and comorbid characteristics in this study shows that without the influence of MTM-based service

Table IV. The influence of MTM-Based Services on Quality of Life for DM Patients

Treatment	Quality of Life Score Average ± up to	Deviation ± SD	P Score
Pre MTM	73.82 ± 7.918	2.605 ± 5.061	0.033
Post MTM	76.42 ± 5.623		

Note * 5% level of confidence (p <0.05); Paired T-Test Analysis

interventions (Pre and Post MTM) there was no difference in each group of disease duration and comorbid characteristics on treatment adherence, with significance values of P = 0.605 and P = 0.977 respectively. It means that there are no influences of disease duration and comorbid characteristics on changes in DM patient compliance scores. This result is similar to the studies conducted by Srikartika *et al.*,[40], that there is no influence of disease duration and comorbidities on DM patient compliance.

Adherence to taking medication is important for DM patients to achieve treatment goals and prevent complications effectively. Good and correct medical therapy will be very beneficial for diabetes patients, especially for patients who are required to take the drug for a long time and for a lifetime. The difference in the results of this study with several previous studies can be due to the lack of the number of patients recruited and the uneven distribution of various characteristic groups, so that it cannot represent the level of adherence to treatment of DM patients. Although the analysis shows that the implementation of MTM-based services by pharmacists influences patient adherence in this study, other factors can also affect the level of adherence after receiving MTM-based services.

The influence of MTM-Based Services on the Quality of Life of the DM Patients

The quality of life of the DM patients is one of the therapeutic goals that must be achieved in DM management because DM is a chronic disease that requires prolonged therapy so that the effectiveness and side effects of the treatment can influence the quality of life of the patient. Assessment of the patient's quality of life uses the DQLCTQ, where the higher the score obtained, the better the quality of life. This study was conducted to see the effect of MTM-based services on the quality of life of the DM patients.

The results of the mean score of quality of life for patients before MTM were 73.82 ± 7.918 to 76.42 ± 5.623 after MTM-based services with the difference obtained was 2.605 ± 5.061. These results show that there is an increase in the quality of life with the significance value obtained is P = 0.033. Statistically, it can be interpreted that there is a difference in the average score of quality of life before and after MTM-based services, or in other words, MTM-based services have an effect on improving the quality of life of DM patients. Data on the influence of MTM-based services on the quality of life of DM patients can be seen in Table IV.

A study regarding the influence of MTM given by pharmacists on the quality of life of DM patients is still rarely conducted. A study that is mostly found is the studies related to the effect of pharmacist intervention other than MTM on improving the quality of life of the DM patients. Some of them are studies conducted by Septiar and Utami[12], revealed that providing counseling by pharmacists for one month increased the quality of life score by p value 0.00 (<0.05), which means that counseling by a pharmacist can improve the quality of life. Adepu *et al.*,[41], also revealed similar results, pharmacists who provide counseling to patients have an impact on improving patient perceptions of disease, lifestyle changes, and overall quality of life in diabetic patients. The counseling given by

pharmacists to patients can be considered as an important element in implementing a DM disease management program[41]. One part of the MTM services is patient education and treatment counseling. Various studies related to the intervention conducted by pharmacists show that with pharmacist intervention, both education and counseling or MTM services can improve the quality of life of the patients.

The improvement of the patient's quality of life can be influenced by various factors, one of which is patient characteristics. In this study, the analysis of the effect of characteristics on changes in the quality of life score of DM patients can be seen in Table V. Based on the analysis of the characteristics of gender and age, it shows that without the influence of MTM-based service interventions (Pre and Post MTM) there is no significant difference in each group of characteristics towards the quality of life of DM patients with a significant value obtained, namely the quality of life of patients, a significance value is obtained respectively, P = 0.185 and P = 0.124. In other words, the results of this study show that there is no effect of gender and age characteristics on changes in the quality of life score of the DM patients. This study is similar to the studies conducted by Ningtyas[42], which shows that there is no effect of gender and age on the quality of life of type 2 DM patients. Meanwhile, Gautam *et al.*,[43], in its studies showed that women have a significantly lower quality of life than male patients. Men have a better quality of life compared to women, maybe because men are more accepting of the reality of diabetes, and have fewer complaints than women so that it affects their quality of life.[21]. Based on age, Adikusuma *et al.*,[21], also show a similar result in that there is no significant effect of age on the quality of life of the respondents with a significance value of p> 0.05. Redekop *et al.*,[44], in its studies stated that patients with age more than 70 years, have the lowest quality of life than others, while the highest quality of life in patients aged less than 50 years. Younger people have a better quality of life because younger people have a more positive attitude towards their outlook on life than older patients[44].

Based on the level of education, it shows that without the influence of MTM-based service interventions (Pre and Post MTM) there is no significant difference in each group of characteristics towards the quality of life of DM patients with a significant value obtained, namely P = 0.090. These results indicate that there is no influence of educational level characteristics on changes in the quality of life score of DM patients. In contrast to the study conducted by Ningtyas[42], where the results of the education level factor analysis using logistic regression test obtained P = 0.02 with an Odds Ratio of 1.9 and 95% Confidence Interval (1.11-3.09). These results indicate that there is an influence between the level of education and the quality of life of patients with type 2 diabetes mellitus, where type 2 diabetes mellitus patients who have a low level of education (elementary school) have a 1.9 times greater risk of having a lower quality of life (no satisfied) than those with higher education (SMA, College / Academy)[42]. On average, patients with low quality of life scores are patients with a lower level of education. Education is an important factor in improving the quality of life, because patients with good education will understand self-care and diabetes management, glycemic control, and self-assessment perceptions.[45].

The results of the analysis of job characteristics also showed that without the influence of MTM-based service interventions (Pre and Post MTM) there was no difference in each characteristic group on the quality of life of DM patients with a significance value obtained, namely P = 0.626, meaning that there was no effect of job characteristics on changes in the quality of life score of DM patients. These results diverge from studies conducted by Zyoud *et al.*,[46] that patients who are unemployed have significantly lower quality of life scores. This finding is consistent with the results reported by Javanbakht *et al.*,[47] based on the quality of life score which indicates that

Table V. The Effect of Characteristics on Changes in the Quality of Life Score of DM Patients

Characteristics	Amount (N)	Change in Score (Δ) Quality of Life	P Score
Gender			
Male	5	6.10	0.185
Female	15	1.44	
Age			
< 45 years	4	6.85	0.124
45-54 years	6	2.53	
55-64 years	8	0.89	
65-74 years	2	1.20	
Last education			
Elementary School	5	2.70	0.090
Junior High School	5	2.88	
Senior High School	6	4.47	
Diploma/Bachelor Degree	4	-0.65	
Occupation			
Employed	8	5.20	0.626
Unemployed	12	0.87	
Duration of DM (duration of disease)			
< 1 years	4	1.65	0.643
1-5 years	6	5.45	
6-10 years	6	-1.50	
≥ 10 years	4	5.45	
Comorbidity disease			
With comorbids	6	0.87	0.573
Without comorbids	14	3.35	

Note: *The analysis used Ancova Test; level of confidence 5% (P <0.05)

unemployment is associated with a higher likelihood of multiple or problems affecting the quality of life.

Based on the duration of the disease and comorbidities, it shows that without the influence of MTM-based service interventions (Pre- and Post-MTM) there is no significant difference in each group of characteristics towards the quality of life of DM patients with significant values obtained, namely P = 0.643 and P = 0.573. These results indicate that the characteristics of the duration of the disease and comorbidities have no effect on changes in the quality of life score of DM patients. Gautam *et al.*,[43], found that patients who had diabetes duration of more than 5 years had lower quality of life scores in all quality of life domains except in general health and mental health, which may be due to adaptation to a diabetic lifestyle. While, patients with comorbidities such as hypertension, statistically, show poor overall quality of life, health satisfaction, physical health, and psychological domains with lower quality of life scores.[45].

Based on the results of the analysis of the influence of these characteristics, it shows that there is no difference in each characteristic group on the quality of life of DM patients. The improvement of the quality of life in this study was supported by the presence of patient factors who were adherent to their treatment

after being given MTM services by pharmacists at the Public health center. In addition, patients who routinely conduct checkups, a healthy lifestyle, an understanding of the disease, and adequate DM treatment are factors that affect the quality of life of patients. The implementation of MTM-based services can facilitate the implementation of pharmaceutical services such as making it easier for pharmacists to monitor patient therapy, identify problems related to treatment, reduce the risk of adverse events related to drugs and based on study results show that the application of MTM-based services by pharmacists can improve adherence and quality of life of DM patients. So it is hoped that the application of MTM-based services by pharmacists at the Yogyakarta City Public Health Center can be conducted regularly and continuously.

Research Limitations

Researchers admit that this study still has many limitations, including the very limited sample size in this study, a short time interval for implementing and evaluating programs such as MTM services and the absence of a control group used as a comparison in this study. So that it cannot fully represent the success of the applied MTM-based services. In addition, the results from the measurement scale used to measure treatment adherence (MGLS) and the patient's quality of life (DQLCTQ) may have some drawbacks as this depends on the honesty of the study respondents in answering the questionnaire.

CONCLUSION

Medication Therapy Management (MTM) -based services provided by pharmacists to DM patients significantly improved treatment adherence (P = 0.005) and patient quality of life (P = 0.033) DM.

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JMPF Vol. 10 No. 3 : 220-232
ISSN-p : 2088-8139
ISSN-e : 2443-2946

The Usage of Dosing GAMA Application to Evaluate the Appropriateness of Drug Doses in Hospitalized Patients with Renal Impairment

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ABSTRACT

An application named 'Dosing GAMA' has developed for drug doses adjustment in patients with renal and hepar impairment. Dosing GAMA is targeted for clinical Pharmacists to calculate and make dose recommendations for patients, based on renal and hepatic conditions. This study aims to identify the appropriateness of drug dosage adjustment by using Dosing GAMA application in hospitalized patients with renal impairment and to determine the risk factors for the drug dose inappropriateness. This study was a retrospective observational descriptive study, cross-sectional design, used a consecutive sampling technique. The source of the data was Medical Record of hospitalized patients with renal impairment (creatinine clearance ≤50 mL/min) from 2018 of February till 2020 of March in the Academic Hospital of UGM. The names and the doses of the drugs were filled to Dosing GAMA application, and it would evaluate the appropriateness of drug doses. There were 570 drugs of 73 medical records included in this study. This study revealed Dosing GAMA could assess 144 drugs (25,6%) need to adjust, and 82 drugs (56,9%) were inappropriate doses. There were significant correlations of the age characteristic (p=0,000) and the creatinine clearance value (p=0,012) to the drugs dose appropriateness. There were inappropriate doses need to adjust in the hospital. So, the use of health-based technology expected for pharmacists to improve the use of drugs rationally.
Keywords: *Dosing GAMA Application; Drug Dose Adjustment; Renal Impairment*

INTRODUCTION

According to the results of Riskesdas in 2018, the prevalence of chronic kidney disease increases from 2% (2013) to 3.8% (2018)[1,2]. Patients with decreased kidney function will affect the elimination of drugs that are excreted through the kidneys and other pharmacokinetic processes. Thus, individual dose adjustment based on creatinine clearance values or glomerular filtration rate using special calculations need to be made in patients with decreased renal function to avoid undesirable effects. Irrational dosing will lead to drug toxicity or ineffectiveness[3].

PERMENKES RI No 72 of 2016 regarding the Standard of Pharmaceutical Services in Hospitals states that a pharmacist, in carrying out clinical pharmacy services, must assess the rationality of the drugs prescribed[4]. However, in reality, irrational administration of drug doses to patients with decreased renal function is still common[5]. This may result in the patient's clinical outcome not improving. Based on the results of the previous studies, there were several factors that influenced the suitability of the dosage given to patients with decreased kidney function, namely gender[6], age[7,8], patients with hemodialysis[9], the amount of drug used, and serum creatinine levels[8].

A computer-based marker system used for dose assessment is a complementary tool for pharmacists[10]. In 2018, a research team from the Laboratory of Pharmacology and Clinical Pharmacy UGM, Rahmawati *et al.*, had developed a Dose Adjustment Software for Patients with Decreased Kidney and Hepatic Function: Dosing GAMA. The Dosing GAMA application has obtained an Intellectual Property Rights (Hak Kekayaan Intelektual) certificate with registration number 000127903[11]. The development of this application was intended to facilitate health workers, especially clinical pharmacists in hospitals, in calculating and recommending dosages according to the patient's kidney and liver condition. At the moment, the Dosing GAMA application is still in the stage of

refinement through several test stages before being widely used. The Dosing GAMA application can be easily accessed via a computer or smart phone connected to the internet. This application is equipped with features such as a login and logout system, a dashboard, data management and patient visits, and drug data settings. The Dosing GAMA is also equipped with facilities for calculating Body Mass Index (BMI), Body Surface Area (BSA), and Creatinine Clearance (CrCl) with the Cockcroft Gault formula automatically, as well as monitoring information on drug use therapy that can be used as a reference for users to perform monitoring the effectiveness of therapy. Determination of the dosage recommendation for Dosing GAMA is available in two criteria, namely based on reference and calculation of pharmacokinetic formulas that are adjusted to individual pharmacokinetic parameters using the Giusti - Hayton method.

Several studies had been conducted regarding the Dosing GAMA Application. Research conducted by Hajma (2020), regarding the use of Dosing GAMA in a group of pharmacists in making dose adjustments, showed that the use of the Dosing GAMA application had been proven to reduce the time to evaluate the dose adjustment by an average of 13.81 ± 0.781 minutes. This time was shorter than the pharmacist who evaluated the dose adjustment manually (without using the application), which was 27.50 ± 1.23 minutes ($p < 0.05$). In addition, based on the results of the usefulness test for Dosing GAMA using the Post-Study System Usability Questionnaire (PSSUQ), it showed its high benefit and was able to be accepted by pharmacists[12]. However, studies regarding the use of this computer-based system in dose adjustment in hospitalized patients with decreased renal function have not been carried out. The purpose of this study is to identify the suitability of drug doses using the Dosing GAMA Application in hospitalized patients with decreased kidney function. This study also aims to determine the factors that influence the emergence of drug dose mismatch problems in hospitalized patients with decreased kidney function.

METODE

Research Design

This research is a descriptive observational study with a cross-sectional study design. The data were collected retrospectively.

The subject of research

The sampling was done using a consecutive technique.

The consecutive technique is one of the non-probabilistic sampling methods, in which includes every patient who meets the study criteria as the study sample.[13] The data was collected through tracing the medical records of inpatients at UGM Hospital Yogyakarta for the period February 2018-March 2020. The criteria for the patient medical records in this study were patients with decreased renal function (creatinine clearance value ≤ 50 mL/min) and patient age ≥18 years. In this study, 73 medical records were obtained with 107 serum creatinine examination data (in one patient's medical record it could consist of one or more serum creatinine tests) with a total of 790 drugs used. A total of 220 names of drugs were not listed in the Dosing GAMA application. Therefore, the dosage suitability evaluation was carried out on a total of 570 drugs using the Dosing GAMA application.

Evaluation of dose suitability using the Dosing GAMA application

The dosage suitability evaluation was carried out using the Dosing GAMA application. To open the Dosing GAMA application, logging in using the appropriate user and password was needed. Patient data was then added to the 'add patient' application menu including the patient's name (initials), sex, and date of birth. Then, in the 'add visit' menu, information on the patient's visit date, serum creatinine, body weight, and diagnosis

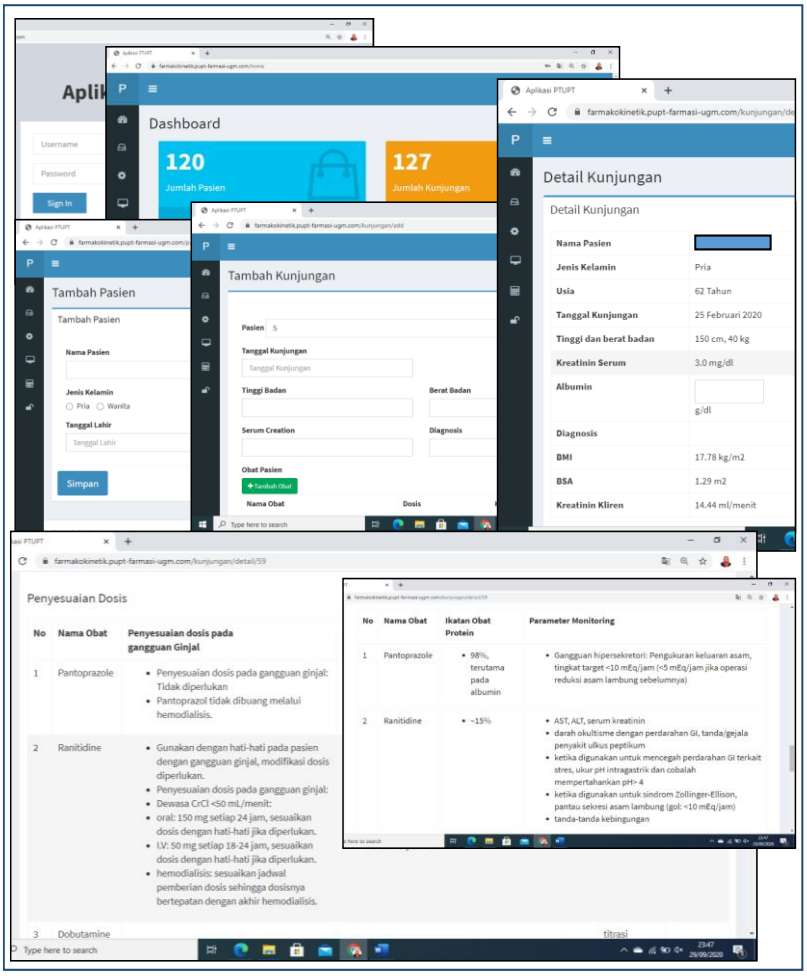

Figure 1. Example of a dosage suitability evaluation display using Dosing GAMA application

was added, as well as drug use data including the name of the drug, the drug dosage, and additional information needed. The results of data that had been entered in the application can be seen in the 'visit details' menu. The dosage recommendations based on the information given will be displayed automatically in the table of 'dose adjustment in renal impairment' in the Dosing GAMA application. In addition, this application will also display information on the appropriate drug use monitoring parameters. Figure 1 shows the information on the Dosing GAMA application in the process of evaluating drug dose adjustments in patients with renal and hepatic disorders.

Data Analysis

The collected data were analyzed using descriptive statistics to present the results of the drug dose assessment and the bivariate test to determine the relationship between dose suitability and patient characteristic data, using Statistical Product and Service Solutions (SPSS).

RESULTS AND DISCUSSION

Data Characteristics

In this study, a total of 570 drugs were evaluated for their suitability using the Dosing GAMA application. A total of 144 drugs were identified requiring dose adjustments. The result of the analysis using the application showed that the dosage was in accordance

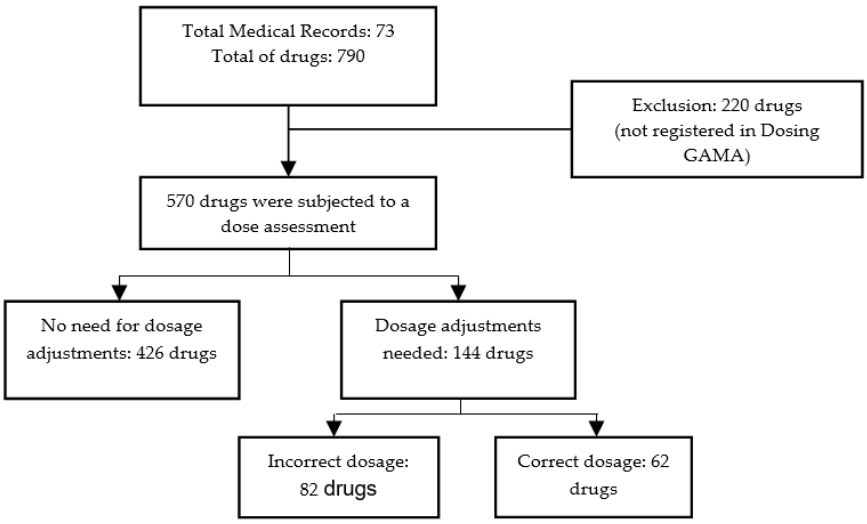

Figure 2. The number of research subjects on the evaluation of dose suitability using Dosing GAMA application

with the calculation results of 62 drugs (Figure).

Table I displays the data on the characteristics of inpatients with kidney disorders used in this study. These characteristic data include: sex (female and male), age (18-60 years and >60 years), treatment room (non-ICU and ICU), Creatinine Serum (SCr), Creatinine Clearance (CrCl), Glomerular Filtration Rate (eGFR) estimation criteria, and diagnosis. Creatinine clearance was calculated using the Cockcroft-Gault equation while eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation.

Based on gender characteristics, there were 51 RM (59.9%) from male gender. This is in line with the previous studies that patients with kidney problems were male[8,14,15]. In this study, 12 out of 20 patients who experienced CRF were male. According to the research conducted by Chang dkk. (2016), this could be related to the presence of risk factors that occur in male patients with CRF in the form of proteinuria, age, anemia, and uncontrolled blood pressure. However, in this study, further analysis related to these risk factors could not be carried out.

Characteristics of age in this study were categorized into elderly (>60 years) and non-elderly (18-60 years). This was based on the criteria for elderly patients issued by the Indonesian Ministry of Health where elderly patients are patients with an age above 60 years[17,18]. The average age for this study was 61.82 years, consisting of 56.2% (41 RM) with age criteria>60 years (Table I). This is in line with previous studies that patients with kidney problems were patients >60 years[14]. Elderly patients have a higher risk of experiencing decreased kidney function due to the decreased ability of organ function in the body[19,20], and have a health status that is dominated by multimorbidity, malnutrition, and organ failure[21].

Patients who are treated in the Intensive Care Unit (ICU) are patients with critical conditions and have multiple organ damage, one of them is the kidney. Organ dysfunction is a common condition in patients admitted to the ICU. The common organ dysfunctions or failure include pulmonary, cardiovascular, renal, hepatic, hematology, and central nervous system[22]. In this study, 74% of the data were obtained from non-ICU care rooms (internal medicine units) and 26% of the data

Table I. Characteristics of patients with impaired kidney function at RSA UGM

Characteristics	n	%	Average ± SD
Gender			
Female	22	30.1	
Male	51	69.9	
Age (years)			61.82 ± 14.842
18-60 years	32	43.8	
>60 years	41	56.2	
Ward			
Non-ICU	54	74	
ICU	19	26	
SCr (mg/dL)			3.39 ± 2.99
CrCl (mL/min)			25.49 ± 11.97
eGFR Criteria (mL/min/1.73m²)			
30-59	37	50.7	
15-29	18	24.7	
<15	18	24.7	
Diagnosis			
Diabetes Mellitus	48	65.8	
Hypertension	37	50.7	
Anemia	20	27.4	
Chronic Renal Failure	20	27.4	
Pneumonia	19	26	
Congestive heart failure (CHF)	18	24.7	
Urinary Tract Infection	14	19.2	
Acute renal failure (ARF)	13	17.8	
Hyperurisemia	11	15.1	
Ischemic heart disease (IHD)	10	13.7	
Hypokalemia, hyperkalemia	9	12.3	
Cerebrovascular Disease	8	11	
Hepatitis	6	8.2	
Hyperlipidemia	3	4.1	
Gallstones	3	4.1	
Cirrhosis of the liver	2	2.7	
Cirrhosis of the liver	1	1.4	

Note: SD = Standard Deviation; SCr = serum creatinine; ICU = Intensive Care; Unit; CrCl = Creatinine clearance (mL/min); n = number of patient medical records (73)

came from ICU care rooms. The number of ICU patients was recorded to be less than the non-ICU patients because the total number of patients admitted to the ICU was relatively less than non-ICU patients.

Creatinine is a product of muscle metabolism which is mainly eliminated by glomerular filtration[23], as the basis for determining the creatinine clearance value. The higher the creatinine value, the more serious the condition of decreased kidney function is. The serum creatinine mean value in this study was 3.39±2.99 mg/dL with an average creatinine clearance (CrCl) value of 25.49±11.97 mL/min. If calculated based on the GFR value, the majority of the samples were in

the range of 30-59 mL/min/m^2, which was 37 samples (50.7%).

As many as 27.4% patients were patients with CRF, acute renal failure (ARF) (17.8%), heart disease (42.5%), hyperuricemia (15.1%), infection (37%), and hypertension (50.7%), and diabetes mellitus (65.8%). The presence of diabetes mellitus, urinary tract infection disorders, cardiovasular disease, and ARF are risk factors for impaired kidney function. In addition, hypertension[16], cardiovascular disease, and ARF itself will also worsen kidney function conditions[24]. The patients with hypertension have a greater risk of developing End Stage Renal Disease (ESRD) and death than patients without hypertension[25].

Drug Dosage Assessment

Based on the results of the assessment of the Dosing GAMA application, there were 144 drugs (25.6%) that were deemed necessary to adjust the dose and 426 drugs (74.4%) were deemed not necessary to adjust the dose. A total of 82 drugs (56.9%) were assessed as having an inappropriate dose and 62 drugs (45.1%) were assessed as having an appropriate dose (Figure). These results indicate that the problem of drug dose adjustment in patients with kidney disorders is still found in clinical practice. The previous studies mentioned that the percentage of drug dose mismatch in patients with impaired kidney function was quite diverse, ranging from 13% to 81%. A study in Lebanon found 49% dose mismatch[9]. Several other countries such as Norway identified 45.5%[26]; China 15.18%[27]; India 81.11%[15]; Iran 54.4%[28]; Malaysia 53%[29]; Pakistan 58.2%[30]; and Indonesia (Jakarta) 13.5%[31]. The diversity of these data may be influenced by the role of doctors and clinical pharmacists in administering and evaluating therapeutic doses for patients with decreased renal function[32,33].

Table II describes the evaluation results of the dose suitability assessment using the Dosing GAMA application along with the type of drug that requires dosage adjustment in patients with kidney disorders.

In this study, it was found that, most of the drugs that required dose adjustment for patients with impaired renal function, included: cardiovascular drugs (26.4%); hyperuricemia (13.9%); antibiotics (11.8%); analgesics (11.8%); diuretics (11.1%); gastrointestinal drugs (8.3%). Types of drugs that were often given in inappropriate doses were cardiovascular drugs (31.7%), antibiotics (13.4%), analgesics (14.6%) and gastrointestinal drugs (14.5%). Similar to the results of previous studies, the drugs most frequently assessed for having Drug Related Problems (DRPs) in patients with impaired renal function are cardiovascular drugs, antimicrobials, antidiabetics, diuretics, allopurinol, ranitidine, metoclopramide[15,28–30,34]. The large number of uses of these drugs in this study was consistent with the diseases suffered by patients, such as cardiovascular disease, including hypertension (50.7%) and other cardiovascular diseases such as CHF and IHD (42.5%); diabetes mellitus (65.8%), hyperuricemia (15.1%), infections (37%), and liver diseases (9.6%).

Irrational use of drug doses is one of the factors that can affect the outcome of therapy, such as drug toxicity or ineffectiveness[3]. For example, in one case there was an increase in the serum creatinine level on the use of ketorolac 30mg/8 hours after the second day, from 1.56mg/dL to 2.37mg/dL. In this case, Dosing GAMA recommends giving ketorolac with a maximum dose of 60mg/day.

In Table III provides recommendations for drug doses based on the Dosing GAMA application. Dosing GAMA uses the Drug Information Handbook as a reference for dosage recommendation data.

Drugs for cardiovascular disease

Tranexamic acid is an antifibrinolytic. More than 95% of the drug will be excreted in the urine[35]. In this study, it was found that 13 times the injection was given at a dose of 500mg/8 hours and one oral distribution with a dose of 3x100mg. Dosing GAMA recommends injection of tranexamic acid at a dose of 10% of the normal dose in patients

Table II. Drug dose assessment based on Dosing GAMA

Drug classes	Drug names	Dose Appropriate		Dose Inappropriate		Total	
		n	%	n	%	n	%
Cardiovascular drugs	*Tranexamic Acid*	0	0	14	17.1	14	9.7
	Bisoprolol	7	11.3	0	0	7	4.7
	Candesartan	0	0	10	12.2	10	6.9
	Captopril	1	1.6	0	0	1	0.7
	Clonidine	0	0	1	1.2	1	0.7
	Digoxin	1	1.6	0	0	1	0.7
	Aspirin	3	4.8	1	1.2	4	2.8
Total		**12**	**19.4**	**26**	**31.7**	**38**	**26.4**
Antibiotics	*Ceftazidime*	0	0	4	4.9	4	2.8
	Cefixime	0	0	2	2.4	2	1.4
	Gentamycin	1	1.6	0	0	1	0.7
	Levofloxacin	0	0	5	6.1	5	3.5
	Meropenem	5	8.1	0	0	5	3.5
Total		**6**	**9.7**	**11**	**13.4**	**17**	**11.8**
Antidiabetics	*Glimepiride*	2	3.2	0	0	2	1.4
	Metformin	0	0	5	6.1	5	3.5
Total		**2**	**3.2**	**5**	**6.1**	**7**	**4.9**
Analgesics	*Ketorolac*	2	3.2	5	6.1	7	4.7
	Paracetamol	2	3.2	7	8.5	9	6.3
	Codeine	1	1.6	0	0	1	0.7
Total		**5**	**8.1**	**12**	**14.6**	**17**	**11.8**
Diuretics	*Mannitol*	0	0	2	2.4	2	1.4
	Furosemide	8	12.9	0	0	8	5.6
	Spironolactone	4	6.5	2	2.4	6	4.2
Total		**12**	**19.4**	**4**	**4.9**	**16**	**11.1**
Gastrointestinal drugs	*Ranitidine*	**0**	**0**	**12**	**14.6**	**12**	**8.3**
Antiemetic	*Metoclopramide*	**5**	**8.1**	**3**	**3.7**	**8**	**5.6**
Antigout	*Allopurinol*	**20**	**32.3**	**0**	**0**	**20**	**13.9**
Antihistamines	*Cetirizine*	**0**	**0**	**3**	**3.7**	**3**	**2.1**
Cholesterol drugs	*Fenofibrate*	**0**	**0**	**3**	**3.7**	**3**	**2.1**
Nervous system drugs	*Gabapentin*	**0**	**0**	**3**	**3.7**	**3**	**2.1**

Note: n = drugs amount; % = drugs amount percentage

with CrCl 10-50 mL/min or 10 mg/kg/dose every 48 hours and 15 mg/kg/dose every 48 hours for oral distribution.

The antihypertensives used in this study include: bisoprolol, candesartan, captopril, and clonidine. Angiotensin-converting enzyme (ACE) inhibitor and Angiotensin Receptor Blocker (ARB) are first-choice drugs for hypertension with type 1 or 2 diabetes mellitus, as well as proteinuria or early chronic kidney disease. This agent can reduce blood pressure and proteinuria with slow progression to the incidence of kidney disease, and is safe for the cardiovascular system. However, Dosing GAMA assesses that candesartan use is contraindicated in patients with CrCl <30 mL/min. Meanwhile, the drugs belonging to the hydrophilic beta blocker

(bisoprolol) and clonidine are considered safe for patients with impaired renal function, but still require dose adjustments[36].

Antidiabetics

Dosing GAMA does not recommend metformin for patients with serum creatinine levels > 1.5 mg/dL for male patients and > 1.4 mg/dL for female patients. As much as 90% of the drug will be excreted through the kidneys. In addition, in some cases metformin distribution will increase lactic acidosis. If necessary, it can be started at a low dose by monitoring the patient's response and tolerance. If there is an indication that the patient has sepsis, then the distribution of metformin should be stopped[36].

Antibiotics

Ceftazidime, cefixime, gentamycin, levofloxacin, and meropenem are antibiotics that are eliminated through the kidneys. Ceftazidime and cefixime are third generation of cephalosporin antibiotics. As much as 80-90% ceftazidime will be excreted in urine. In patients with decreased renal function, ceftazidime will have an extended half-life [35]. Dosing GAMA recommends giving ceftazidime every 12 hours for patients with CrCl values 30-50 mL/min and every 24 hours for patients with CrCl values 10-30 mL/min.

Cefixime has protein binding as much as 65% as well as an extended half-life in patients with impaired renal function up to 11.5 hours from normal conditions 3-4hours, so it is necessary to reduce the dose [35]. The recommended dose of cefixime by Dosing GAMA for patients with CrCl 21-60 mL/min or on hemodialysis is 75% of the standard dose.

Levofloxacin is a fluoroquinolone antibiotic. Levofloxacin will be excreted in urine (~87% in whole form). An extended half-life will occur in patients with CrCl values of 20-49mL/min (27 hours) and <20mL/min (35hours) [35]. Dosing GAMA recommends giving a dose of 750 mg/48 hours in patients with a CrCl value of 20-49 mL/min.

Analgesics

Paracetamol is a non-opioid analgesic which is considered safe for patients with impaired renal function. Dosing GAMA recommends giving a dose of 500mg every 6 hours for patients with a GFR of 10-50 mL/min/1.73m^2. While ketorolac is a Nonsteroidal anti-inflammatory drug (NSAID) analgesic with side effects such as acute renal failure, nephrotic syndrome with interstitial, and chronic renal failure with or without glomerulopathy, intertisial nephritis, and papillary necrosis. The risk of developing acute renal failure was 3 times higher in patients taking NSAID compared to those who did not [36]. Dosing GAMA recommends giving a dose of 30mg/12-24hours or 15 mg/6h in patients with a CrCl value of 10-50 mL/min.

Diuretics

Spironolakton is a potassium-sparing diuretic. Concomitant use with thiazide, furosemide or both may prevent hyperkalemia. Mannitol is an osmotic diuretics[35]. Dosing GAMA contraindicates mannitol use on patients with chronic renal impairment. Dosing GAMA recommends spironolactone given every 12-24 hours for patient with CrCl 10-50 mL/min.

Ranitidine

Ranitidine injection will be excreted through feces by 70% and its half-life is prolonged on patients with renal function impairment [35]. Dosing GAMA recommends 50 mg/18-24hours dosage of ranitidine for patients with CrCl <50mL/min. Inappropriate dosage found in this research is that ranitidine was injected every 12 hours, which is inappropriate in terms of frequency.

Metoclopramide

Metoclopramide is antiemetics drug from dopamine antagonist category. It will be excreted through urine by ~85%. Half-life of this drug depends on the prescribed dose, that is 5-6 hours for adult patients. The AUC will

Table III. Dosage recommendations based on Dosing GAMA

Drug Names	Amount (n)	Dosage given	Drug route	Dosing GAMA	
				Information	Recommendation
Tranexamic acid	13	500mg/8hours	Inj	CrCl 10-50 mL/min	10xkg Body Weight/ 48hours
	1	3x100mg	PO	CrCl 10-50 mL/min	15xkg Body Weight every 48hours
Candesartan	6	1x16mg	PO	CrCl<30mL/min	Contraindicated
	4	1x8mg	PO		
Clonidine	1	1x0.5mg	PO	CrCl <10 mL /min	2x0.05-0.1mg
Ceftazidime	1	1g/8hours	Inj	CrCl 30-50 mL/min	1g/12hours
	1	1g/8hours	Inj	CrCl 10-30 mL/min	1g/24hours
	2	1g/12hours	Inj		
Cefixime	2	2x200mg	PO	CrCl 21-60 mL/min or by hemodialysis	1x300mg or 2x150mg
Levofloxacin	4	750mg/ 24hours	Inj	CrCl 20-49 mL/min	750mg/48hours
Metformin	3	3x500mg	PO	SCr > 1.5 mg/dL in men, or > 1.4 mg/dL in women	Contraindicated
	1	1x500mg	PO		
	1	2x500mg	PO		
Ketorolac	5	30mg/8hours	Inj	GFR 10-20 mL/min/1.73m^2	30mg/12-24hours or 15mg/6hours
Paracetamol	7	3x500mg	PO	GFR 10-50 mL/min/1.73m^2	4x500mg
Mannitol	2	125mL/ 6hours	Inj	GFR <10 mL/min/1.73m^2	Contraindicated
Spironolactone	1	2x100 mg	PO	CrCl 10-50 mL/min	1-2x12.5-25mg
	1	1x100 mg	PO		
Ranitidine	9	25mg/ 12hours	Inj	CrCl <50mL/min	50 mg/18-24hours
	3	50mg/ 12hours	Inj		
Metoclopramide	3	10mg/8hours	Inj	CrCl < 40 mL/min	5mg/6-12hours
Fenofibrate	1	1x300mg	PO	GFR <30 mL/min/1.73 m^2	Contraindicated
	1	1x100mg	PO		
	1	1x150mg	PO		
Gabapentin	1	1x300mg	PO	CrCl> 30-59 mL/min	2x200mg
	1	2x100mg	PO		
	1	1x100mg	PO		
Cetirizine	3	1x10mg	PO	CrCl 11-31 mL/min	1x5mg

Note: Drug route = drug distribution route; Inj = Injection; PO = Per-Oral; CrCl = Creatinine Clearance; GFR = Glomerular Filtration Rate

Table IV. Demographic data effect on dose assessment

Parameter	Total Drug		*p-value*	Odds Ratio (CI 95%)
	Dose Inappropriate n (%)	Appropriate n (%)		
Gender				
Female	24 (66.7)	12 (33.3)	0.174	1.724 (0.783-3.797)
Male	58 (53.7)	50 (46.3)		
Age Category				
>60 years	53 (71.6)	21 (28.4)	0.000*	3.568 (1.783-7.142)
18-60 years	29 (41.4)	41 (58.6)		
CrCl				
<30 mL/min	58 (65.9)	30 (34.1)	0.006*	2.578 (1.295-5.133)
≥30 mL/min	24 (42.9)	32 (57.1)		
Total Drug				
>5 drugs	65 (56.0)	51 (43.9)	0.621	0.825 (0.355-1.915)
≤5 drugs	17 (60.7)	11 (39.3)		

Note: CrCl = creatinine clearance; *Chi-Square test with <0.05 significance; CI = Confidence Interval

increase on patients with renal function impairment, even as much as 2 times higher for patients under acute to chronic category[35]. Dosing GAMA recommends 50% normal dose of metoclopramide prescribed for patients with CrCl < 40 mL/min.

Cetirizine

Cetirizine has 93% protein binding with 8 hours half-life, and will be excreted through urine by 70% [35]. Dosing GAMA recommends 5mg/day dosage of cetirizine for patients with CrCl 11-31 mL/min.

Fenofibrate

Fenofibrate has ~99% protein binding. The half-life is 20 hours on patients with normal renal condition, and will be increased along with the functional impairment condition. 0% of this drug will be excreted through urine[35]. Dosing GAMA contraindicates the use of fenofibrate on patients with GFR <30 mL/min/1.73 m^2.

Gabapentin

Gabapentin is anticonvulsants or GABA analogue drug, has <3% protein binding with 5-7 hours half-life on patients with normal renal function. The half-life will increase along the renal function impairment severity [35]. Dosing GAMA recommends the following gabapentin dose: CrCl> 30-59 mL/min: 2x (200-700 mg); CrCl> 15-29 mL/min: 1x (200-700 mg); CrCl 15 mL/min: 1x (100-300 mg); and CrCl<15 mL/min: professionally decreased dose based on creatinine clearance value.

Dose Assessment Affecting Factors

The following is the result of factor analysis that is expected to affect the result of drug dose assessment.

Based on bivariate analysis (Table IV), it was found that there is no significant correlation between gender and total drug prescribed. However, there is significant correlation between age and creatinine clearance value to drug dose adjustment ($p<0.05$). Patients who are >60 years have 3.568 times higher risk of getting inappropriate drug dose prescription, while patients with CrCl value <30mL have 2.578 times higher risk of getting inappropriate drug dose prescription. This is in accordance with research by Breton dan rekan (2011)[7] and Saad (2019)[9] that

conclude elderly patients have higher risk of getting inappropriate drug dosage prescription. On the other hand, a research by Getachew dan rekan (2015) claimed that creatinine serum value has significant correlation with drug dosage adjustment prescribed to patient with renal impairment[8]. This is as elderly patients have higher risk of renal impairment due to the organ function impairment [19,20], following health status dominated by multimorbidity, malnutrition, and organ failure[21], that it causes increased drug dose and affects drug dosage adjustment.

From this research, it is concluded that by using Dosing GAMA application, clinical pharmacist in the hospital may have drug dose adjustment based on the patient's renal condition. Even so, this research have limitations. By using retrospective data, no real time intervention was possible on the drug prescription, the relatively small number of research sample, and also there were certain clinical consideration from the doctor and/or clinical pharmacist in the hospital that made different drug doses interpretation unavoidable. Furthermore, there are just limited drugs registered in Dosing GAMA. In this research, 19 drugs were not registered and in need of dose adjustment based on the renal impairment severity.

CONCLUSION

Dosing GAMA application is able to identify dose adjustment on 144 drugs from 570 drugs (25.6%) with 56.9% (82 drugs) are inappropriate dose. There is significant correlation (p<0.05) between age characteristic data (OR 3.568 (CI 95%: 1.783-7.142)) and CrCl value (OR 2.578 (CI 95%: 1.295-5.133)) to the therapy adjustment dose. There were problems found on the drug dose adjustment for renal impairment patient in clinical practice. Pharmacy Support System as in Dosing GAMA application could provide assistance to clinical pharmacy in identifying patient's drug use problem. Age and renal function characteristics of the renal impaired patients should actually be taken into consideration for pharmacist to assess dosage adjustment.

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