In Vitro Comparison of Brand-name and Generic Ceftriaxone: Potency Versus Price

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Abstract

Background Ceftriaxone is a broad-spectrum third-generation cephalosporin antibiotic used to treat many significant infections due to its high antibacterial potential, a broad spectrum of activity, and low toxicity. These antibiotics are prescribed for various infections every day, especially in developing countries. The difference in the price of generic and brand-name ceftriaxone impressed that brand-name drug has better quality than generic. This study aimed to compare brand-name ceftriaxone's quality over generics that have a notable price difference. **Methods**: We presumed all ceftriaxone injections had a similar quality. Escherichia coli ATCC® 25922 with MIC of 0.03-0.12 ug/ml against ceftriaxone was used as the evaluation standard. Using Mueller Hinton agar with serial ceftriaxone concentration double diluted from 0.48 until 0.0075 ug/ml. There were three groups of ceftriaxone, brand-name, generic name, and control (SIGMA Aldrich). A drop of suspension of Escherichia coli ATCC-25922 in 20 µl of 10^4 CFU was applied on the surface medium. After incubation at 37°C overnight, the MIC of the three groups was noted. MIC, as shown in the concentration of 0.03-0.12 ug/ml, was confirmed as good quality ceftriaxone.
Results A total of 11 brand names and 14 generic ceftriaxone injections shared identical MIC at 0.06 µg/ml. Brand-name ceftriaxone overpriced generic with average price 234,400 ($16,32) and 16,686 ($1,16) respectively.
Conclusion: While being sold at a higher price, brand-name ceftriaxone has equivalent in vitro potency to generic.

Keywords ceftriaxone, brand-name, generic, MIC, price.

1. Introduction

Ceftriaxone is a broad-spectrum third-generation cephalosporin antibiotic commonly prescribed to treat various infections and favored in most antibiotic formularies in hospitals across developing countries [1,2]. This drug is used to treat many important infections due to its excellent antibacterial potential, broad spectrum of activity, and low potential for toxicity. However, its superior activity against Enterobacteriaceae was in line with the increasing frequency of beta-lactamase-mediated resistance [3]. Addressing this resistance problem, the actual concentration of active ingredients in the antibiotic itself is crucial [4].

According to the Indonesian Food and Drug Authority registry, 49 ceftriaxone injections were available in the market across Indonesia and in compliance with distribution legality both for brand-name and generic preparations. Moreover, price is ranging from IDR 11,000 ($ 0,77) to IDR 266,000 ($18,52). Slight differences in the concentration of active ingredients may impact the actual efficacy [5,6]. The content of active ingredients is vital to achieving equivalent pharmaceutical activity of generic drugs compared to their innovative products [4,7].

Both doctors and pharmacists believe that the more expensive, the more effective. People tend to think that generic is cheap, lacks quality, and ineffective [8,9]). This thought leads to the overuse of these antibiotics simply because they are more expensive and broad-spectrum, as a result, increasing the occurrence of bacterial resistance cost without any significant benefit [2,8].

This study aimed to compare in vitro potency of various ceftriaxone injections in the market, both generic and brand-name.

2. Material and Method

2.1. Sample

The samples were 14 generics and 11 brand-name ceftriaxone injections from hospitals and pharmacies in Surabaya, Gresik, and Madura, East Java Province, Indonesia. All samples were available in 1gr/vial with an official distribution permit and were not expired. The ceftriaxone was dissolved in sterile distilled water to the concentration of 2 µg/µl. Serial dilution of ceftriaxone was made to obtain a final concentration of 0.0075 µg/ml; 0.015µg/ml; 0.03 µg/ml; 0.06 µg/ml; 0.12 µg/ml; 0.24 µg/ml; 0.48 µg/ml. The study was conducted from November -to December 2020.

2.2. Inoculum

Escherichia coli American Type Culture Collection (ATCC)® 2592 was used as test microorganism to compare the potency of each brand ceftriaxone. Escherichia coli was subcultured from stock on blood agar media, incubated at 35ºC overnight. Following incubation, 4-5 growing colonies were dissolved in 5 ml 0.9% NaCl to fulfil 0.5 McFarland standard with BD Phoenix Spec nephelometer ($1.5x10^8$ CFU/ml). Serial dilution was carried out to attain 10^4 CFU/20µl inoculum [9,10,11,12].

2.3. Anti-bacterial assay

The droplet dilution agar method investigated the potency of ceftriaxone injections [9,12]. In-house Mueller Hinton Agar (MHA) media was dissolved with seven concentrations of each brand of ceftriaxone at a temperature of 50ºC, poured on a 60 mm sterile plate, and allowed to solidify. Afterward, a drop of 20 µl bacterial suspension was inoculated onto MHA containing ceftriaxone, allowed to dry at room temperature, then incubated at 35ºC overnight. Negative growth control was made by MHA without bacterial inoculation, while positive growth by MHA without antibiotics. The assessment was made by placing plates on a dark background without light reflection. The presence or absence of growth of Escherichia coli was observed on each plate. If a single or hazy colony was seen within the inoculation area, it was considered as no growth. The MIC was recorded as the lowest antibiotic concentration at which no bacterial growth was completely absent with unaided eyes. If bacterial growth was at higher concentrations but did not grow at lower concentrations, then a retest was mandatory [9,10,11,12]. Each brand of ceftriaxone was tested in two replicates.

2.4. Analysis

The results were collected as a hard copy and data was analyzed and expressed in the form of tables. Price difference between groups was analyzed by Mann Whitney hypothesis test. All analysis was done using SPSS version 20.

3. Results

Escherichia coli ATCC® 25922 started to grow at a concentration of 0.03 µg/ml (0.48 µg/ml; 0.24 µg/ml; 0.12 µg/ml; 0.06 µg/ml; 0.03 µg/ml; 0.015 µg/ml; and 0.0075 µg/ml) (figure 1-4). All ceftriaxone tested had the same potency in inhibiting the growth of Escherichia coli ATCC® 25922 at MIC 0.06 µg/ml, which exhibited the bioequivalence of generic and brand-name ceftriaxone compared to the control group. Both generic and brand-name products displayed identical in vitro potential antimicrobial activity.

As showed in table 2, the ceftriaxone tested had the lowest price of IDR 11,000 ($0,77) and the most expensive IDR 276,000 ($19,21) with an average of IDR 112,479 ($7,83). The generic ceftriaxone group has the lowest price of IDR 11,000 ($0,77) and the highest was IDR 42,500 ($2,96) with an average of IDR 13.075 ($0,91). While the brand-name ceftriaxone group has the lowest price of IDR 188,980 ($13,15) and the most expensive at IDR 276,000 ($19,21) with an average price of IDR 234,400 ($16,32). Among all ceftriaxone, generic group was below the average price, whereas the brand-name group was higher. Prices below the average were considered cheap, while above were considered expensive. The Mann-Whitney test proved that brand-name ceftriaxone was significantly more expensive than generic with p value of <0.001.

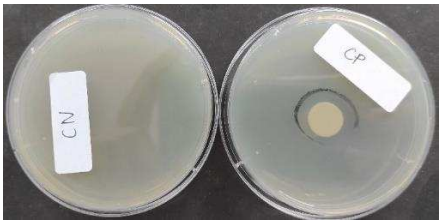

Figure 1 Positive control and negative control. CN: Negative control, CP: Positive control.

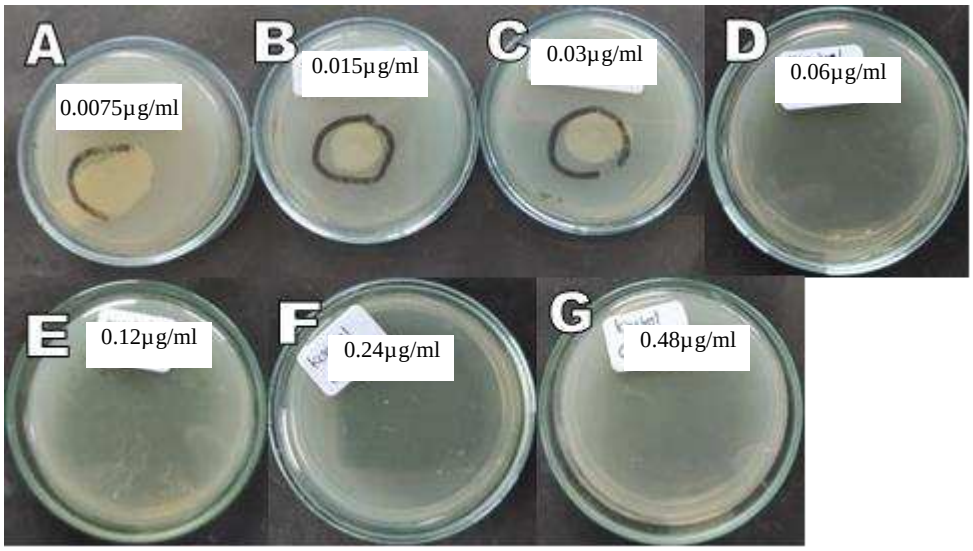

Figure 2 Growth of Escherichia coli ATCC® 25922 on MHA media with each control concentration of ceftriaxone. Escherichia coli ATCC® 25922 started to grow at a concentration of ceftriaxone 0.03 µg/ml.

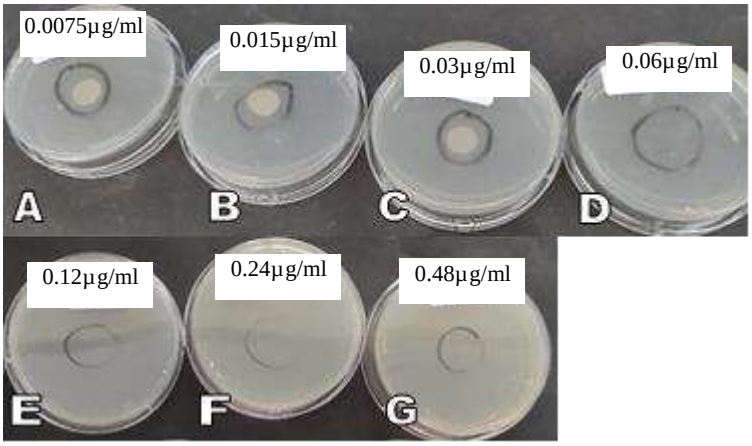

Figure 3 Growth of Escherichia coli ATCC® 25922 on MHA media with each concentration of ceftriaxone. Trade name. Escherichia coli ATCC® 25922 started to grow at a concentration of ceftriaxone 0.03 µg/ml.

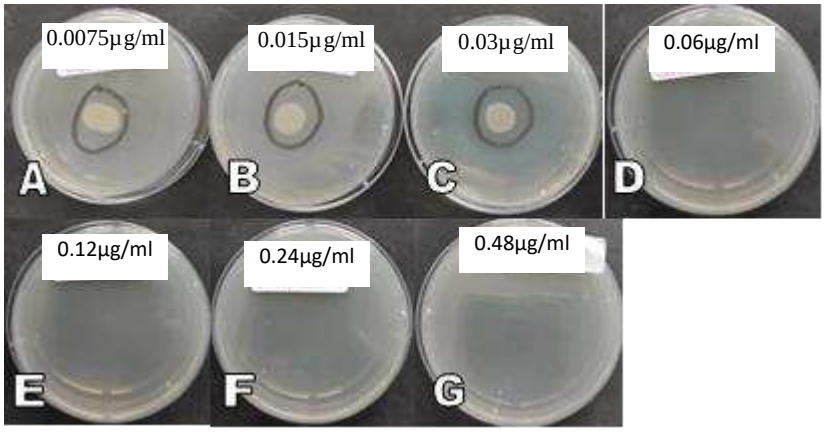

Figure 4 Growth of Escherichia coli ATCC® 25922 on MHA media with each concentration of generic ceftriaxone. Escherichia coli ATCC® 25922 started to grow at a concentration of ceftriaxone 0.03 µg/ml.

Table 1 Distribution of ceftriaxone by group, manufacturer, location of purchase, price, and MIC.

No	Ceftriaxone Group	Manufacture	Batch No	Expired Date	Purchase Location	MIC (µg/ml)
1	Control				USA	0,06
2	Generic	A	ICFRA01216	Oct-22	Surabaya	0,06
3	Generic	A	ICFRA01189	Sep-22	Surabaya	0,06
4	Generic	A	ICFRA01217	Oct-22	Surabaya	0,06
5	Generic	A	ICFRA01191	Oct-22	Madura	0,06
6	Generic	A	ICFRA01217	Oct-22	Gresik	0,06
7	Generic	B	51B0525	Jan-23	Surabaya	0,06
8	Generic	B	51C0102	Feb-23	Surabaya	0,06
9	Generic	B	50I0533	Aug-22	Madura	0,06
10	Generic	B	50H0665	Jul-22	Madura	0,06
11	Generic	B	50H0667	Jul-22	Madura	0,06
12	Generic	B	50B0144	Sep-21	Madura	0,06
13	Generic	B	50H0662	Jul-22	Surabaya	0,06
14	Generic	C	C10317004	Mar-22	Surabaya	0,06
15	Generic	D	PSL45048	Oct-21	Madura	0,06
16	Brand-name	B	51A0358	Dec-22	Surabaya	0,06
17	Brand-name	B	51A0135	Dec-22	Surabaya	0,06
18	Brand-name	B	51A038	Dec-22	Surabaya	0,06
19	Brand-name	E	VBR0K90214	Dec-22	Surabaya	0,06
20	Brand-name	E	VBROK00225	Mar-22	Surabaya	0,06
21	Brand-name	E	VBROK90175	May-22	Surabaya	0,06
22	Brand-name	E	VBRHA90211	May-21	Surabaya	0,06
23	Brand-name	F	ADA611B	Apr-22	Surabaya	0,06
24	Brand-name	F	AD4612	Apr-22	Surabaya	0,06
25	Brand-name	F	AD4611B	Apr-22	Madura	0,06
26	Brand-name	F	A4D611B	Apr-22	Gresik	0,06

Table 2 Distribution of average prices of ceftriaxone injection brand-name and generic

Group	Price		p value
	Median (USD)	Range (USD) (Minimum-Maximum)	
Generic (n=14)	($0,91)	($ 0,77- $2,96)	<0,001
Brand-name (n=11)	($16,32)	($13,15-$19,21)	

Mann-Whitney test. Mean Rank Generic 7,50; Brand-named 20,00.

Note: 1 USD = IDR 14,344.24

4. Discussion

Commercially ceftriaxone injections were circulating in the market and are often used in therapy. Thus, comparative in-vitro efficacy studies provide evaluation to identify counterfeit products and determine different quality between the same product obtained from different manufacturers [8]. There is a need for confirmation of the belief that 'the more expensive the product, the more effective it is'. Numerous people have the thought that brand name drugs are better than generic since generic drugs are sold at low price thus indirectly suggesting its poor quality [8,13]. This induces selective pressure of microbial resistance and increases cost without any real benefit [8,14]. The microbial assay indicates the potency of the ceftriaxone and can reveal subtle alterations that are not demonstrable by convention chemical methods [15]. Bioassays play an essential role in quality control of antibiotic [16]. Microbiological assays are simple, specific, inexpensive, and convenient method [17].

All brands of ceftriaxone tested against Escherichia coli ATCC® 25922 demonstrated equivalent MIC value at 0.06 µg/ml. Based on the CLSI M100, 2019 the MIC of ceftriaxone against Escherichia coli ATCC® 25922 was 0.03-0.12 µg/ml on MHA without supplementation. Study by Gunasekaran et al [8] showed that all brands of ceftriaxone tested against four bacteria had sufficient inhibitory activity compared to CLSI. The result agreed with that reported by Idries and Ibrahim [18] that the potency of tested ceftriaxones were equivalent to the reference product against Staphylococcus aureus ATCC 6538. In contrast with the study conducted by Lourenço et al [15], the tested ceftriaxones failed to meet reference product against Staphylococcus aureus (ATCC 6538). Another study showed the difference of ±20% of bioequivalence between generic and brand preparations [19]. While the study of Liebowita and Slabbert [20] showed a discordance, where the MIC value of generic ceftriaxone was two-fold lower than the original drug.

Basically, generic drugs are one of the pharmaceutical drugs that have met the pharmacopeial requirements and have undergone through the manufacturing process according to good manufacturing practices for drug [13,14]. The price of generic drugs is way cheaper than brand-name drugs because the generic drug industry operates not based on competitiveness, but sales volume [14]. Patent drugs have an average validity period of 15 years, after which the patent period expires, the same drug can be produced by other pharmaceutical companies at a lower price than the original product. Copy products can save production costs up to 15-30% compared to original products. Copy products do not need to carry out special studies to demonstrate the efficacy and tolerability of all possible clinical indications of preclinical and clinical phases. Thus, the company that produces the copy drug only has to pay the production and distribution costs. This is the reason generic products have lower prices when compared to innovator products [13]. Generic drugs do not require to put money on research for innovation because these drugs were previously registered patent. Thus, the price difference of generic and brand-name drugs is only due to reasons above, not because of difference in composition or quality [13, 14].

In this study, it was found that brand-name ceftriaxones are significantly more expensive than the generic products. This is in accordance with the study of Naimi et al in Kabul [21] that the highest price was found for the drugs manufactured by well-known International pharmaceutical companies and the low-price was from local generic companies.

Studies in various biomedical disciplines show that the clinical efficacy of an antibiotic depends on multiple factors, the fundamental one being an adequate bacterial spectrum and the intrinsic antimicrobial activity of the drug. The pharmacokinetic profile of the drug is another important parameter, which at therapeutic doses, allows it to reach high plasmatic and tissue concentrations in the site of infection [13].

The limitation of this study was the low number of ceftriaxone sample.

5. Conclusion

Both generic and brand-name ceftriaxone in East Java region appeared to be equivalent in vitro and therefore, the use of generic ceftriaxone in patient care management will allow reduction of cost without losing its effectiveness.

Conflict of Interest

None declared.

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References

1. Kim, B.N., Peri, A.M., Paterson, D.L. 2018. 'Ceftriaxone', in Grayson, M. (ed.) Kucers' The Use Of Antibiotics. 7th edn. London: Edward Arnold Ltd. 464-529.
2. Lee, K., Lim, J.K., Yong, D., Yum, J., Chong, Y., Okamoto, R., Inoue, M. 2001. 'Evaluation of efficiency of screening extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae in hospitals where the bacteria are increasingly prevalent'. J. Clinic Microbiol. 39(10): pp 3696-99.
3. Dafale, N.A., Semwal, U.P., Agarwal, P.K., Sharma,P., Singh, G.N. 2012. 'Quantification of ceftriaxone sodium in pharmaceutical preparations by a new validated microbiological bioassay'. Anal. Methods. 4, 2490.
4. Dafale, N.A., Semwal, U.P., Rajput, R.K.,Singh, G.N. 2016. 'Selection of appropriate analytical tools to determine the potency and bioactivity of antibiotics and antibiotic resistance'. Journal of Pharmaceutical Analysis. pp207–13.
5. Dafale, N.A., Semwal, U.P., Agarwal. 2015. 'Development and validation of microbial assay for quantification of levofloxacin in pharmaceutical preparation'. J. Pharm. Anal. 5: pp 18-26.
6. Zuluaga, A.F., Agudelo, M., Rodriguez, C.A. 2009. 'Application of microbiological assay to determine pharmaceutical equivalence of generic intravenous antibiotic'. BMC Clin. Pharmacol.
7. Teixeira da Trindade, M., Salgado, H.R.N. 2018. 'A critical review of analytical methods for determination of ceftriaxone sodium'. Analytical Chemistry.48(2): pp 95-101.
8. Gunasekaran,T., Desta, E.D., Seifu, M.F., Gelaw, B.K., Mariam, E.T.G., Ahmed, M. 2015. 'Comparative efficacy evaluation of seven commercial injectable ceftriaxone purchased at Ambo, Oromia regional state, Ethiopia, using agar well plate diffusion method'. JPHSR. 6: pp 97–101.
9. Wiegand, I., Hilpert, K., Hancock, R. E. W. 2008. 'Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances'. Nature Protocols. 3(2): pp 163-165.
10. Leber, A. L. 2016. Clinical Microbiology Procedures Handbook, 4th edition. Washington: American Society for Microbiology.
11. CLSI. 2019. Performance standards for antimicrobial susceptibility testing; twenty-nineth informational supplement. M100-S29 edn. USA.
12. CLSI. 2015. Methods for dilution antimicrobial susceptibility test for bacteria that grow aerobically. M07-A10. Tenth edition. USA.
13. Concia.E., Novelli, A., Schito, G.C., Marchese, A. 2007. 'Ideal microbiological and pharmacological characteristics of a quality antimicrobial agent: comparing original and generic molecules'. Journal of Chemotherapy. 19 (6): pp 609-19.
14. Lambert, P.A., and Conway, B.A. 2003. 'Pharmaceutical quality of ceftriaxone generic drug products compared with Rocephin®'. Journal of Chemotherapy. Vol. 15(4): pp 357-68.
15. Lourenço, F. R., Traple, M. A. L., Okamoto, R. T., Pinto, T. J. A. 2013. Development and Validation of Microbiological Assay for Ceftriaxone and its Application in Photo-stability Study. Current Pharmaceutical Analysis. 9, 77-81.
16. Abdullatif, H. K., El-Ganiny, A. M., El-Adl, A.S.2017. Evaluation of the potency of some antibiotic formulations in the Egyptian market. Zagazig J. Pharm. Sci. Vol. 26 (1): pp 48-54.
17. Bekele L.K., Gebeyehu, G.G. 2012. Application of different analytical techniques and microbiological assays for the analysis of macrolide antibiotics from pharmaceutical dosage forms and biological Matrices: A review. ISRN Analytical Chemistry.
18. Idries, A.M., Ibrahim , K.E. 2014. Microbiological Assay of two selected products of cephtriaxone powder for injection from pharmaceuticals market in Sudan. Sudan Journal of Medical Sciences, 9(4): 251-258.
19. Gallelli, L., Palleria, C., Antonio De Vuono2, Laura Mumoli1, Piero Vasapollo2, Brunella Piro3, Emilio Russo. Safety and efficacy of generic drugs with respect to brand formulation. Journal of Pharmacology and Pharmacotherapeutics

20. Liebowita, L. B., Slabbert, M. 2005. Comparative in Vitro activity of Generic Injectable Cephalosporins. Southern African Journal of Epidemiology and Infection. 20 (3): 82-84. DOI: 10.1080/10158782.2005.11441241.
21. Naimi, H. M., Rasekh, H., Haem Rahimi, M., Yousofi, H. 2016. Assessment of the price-efficacy relationship for multiple brands of ceftriaxone sodium in Kabul: a cross-sectional study. BMC Res Notes. 9 (86): 1-6.