EFFECTIVENESS OF FOSFOMYCIN ON PREVENTION OF SURGICAL SITE INFECTION OF CLOSED BRAIN INJURY PATIENTS AFTER CRANIOTOMY IN EMERGENCY UNIT DR. SOETOMO HOSPITAL

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ABSTRAK

*Antibiotik profilaksis dapat mencegah ILO (Infeksi Luka Operasi) sampai < 5 % ada pasien yang menjalani kraniotomi. Fosfomycin memiliki spektrum aktivitas untuk semua patogen rentan menyebabkan ILO pada kraniotomi (Staphylooccus aureus dan Staphylococcus epidermidis) dan memiliki kemampuan untuk menembus ke dalam CSF dengan atau tanpa kondisi inflamasi pada mninges (rasio fosfomycin AUCCSF/AUCs, tanpa peradangan, adalah 0,09-0,27). Sebuah studi prospektif observasional dilakukan untuk menganalisis efektivitas fosfomycin dalam mencegah infeksi Luka Operasi (ILO) pasca prosedur kraniotomi pada unit gawat darurat RS Pendidikan Dr. Soetomo Surabaya dengan insiden SSI sebagai parameter (superficial, deep atau organ). Kriteria inklusi adalah pasien dengan cedera otak tertutup (ringan, sedang, atau berat), menjalani prosedur kraniotomi tanpa implan, menerima fosfomycin sebagai antibiotik profilaksis (2 x 2 g iv dalam 30-60 menit sebelum operasi bedah), dan 30 hari setelah prosedur kraniotomi luka operasi dievaluasi. Ada 30 pasien yang diperoleh dari penelitian ini. Insiden ILO pada pasien dengan abses subdural (dikategorikan sebagai ILO organ) adalah 3,3%. Faktor risiko yang kebanyakan ditemukan pada pasien dengan ILO adalah riwayat merokok 30 hari sebelum prosedur bedah, meminum obat immunosuppressant, menjalani operasi darurat, durasi operasi > 3,75 jam dan pendarahan Volume ≥ 1500 mL. Bakteri yang menyebabkan ILO adalah Pseudomonas aeruginosa yang sensitif terhadap fosfomycin, piperasilin tazobactam, dan meropenem. LOS pasien dengan ILO 3x lebih lama daripada tanpa ILO. Fosfomycin efektif mencegah ILO pada pasien dengan prosedur postcraniotomy cedera otak tertutup pada unit gawat darurat RS Pendidikan Dr. Soetomo Surabaya.**(FMI 2014;50:153-159)***

***Kata kunci:** cedera otak tertutup, kraniotomi, infeksi luka operasi, fosfomisin*

ABSTRACT

Prophylactic antibiotics can prevent SSI (Surgical Site Infection) until < 5% in patients undergo craniotomy. Fosfomycin has spectrum of activity for all susceptible pathogens of SSI in craniotomy (Staphylococcus aureus and Staphylococcus epidermidis) and has the ability to penetrate into CSF with or without inflammation condition of meninges (fosfomycin AUCCSF/AUCs ratio, without inflammation, is 0.09–0.27). An observasional prospective study was conducted to analyze the effectiveness of fosfomycin in preventing surgical site infection (SSI) post craniotomy procedure at emergency unit of Dr. Soetomo Teaching Hospital Surabaya with incidents of SSI as the parameters (superficial, deep or organ). Inclusion criteria were patients with closed brain injury (mild, moderate, or severe), underwent craniotomy procedure without implant, received fosfomycin as prophylactic antibiotic (2 x 2 g iv within 30–60 minutes prior surgical operation), and 30 days after craniotomy procedure, the surgical sites were evaluated. There were 30 patients obtained from this study. The incidence of SSI in patients with subdural abcess (categorized as organ SSI) was 3,3%. Risk factor found mostly in patient with SSI were smoking history 30 days before surgical procedure, taking immunosuppressant agents, undergo emergency surgery, operating duration > 3,75 hours and bleeding volume ≥ 1500 mL. Bacteria causing SSI was Pseudomonas aeruginosa which is sensitive to fosfomycin, piperacillin tazobactam, and meropenem. LOS patient with SSI 3x longer than without SSI. Fosfomycin effectively prevented SSI in patients with closed brain injury postcraniotomy procedure at emergency unit of Dr. Soetomo Teaching Hospital Surabaya. ***(FMI 2014;50:153-159)***

***Keywords:** closed brain injury, craniotomy, surgical site infection, fosfomycin*

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INTRODUCTION

Brain injury remains a serious problem in Indonesia, particularly in hospitals Dr. Soetomo (Wahyuadi et al 2007, Wahyuhadi 2010). The high mortality rate in patients with brain injury caused by intracranial hematoma formation can be prevented with hematoma evacuation via craniotomy. The most common complications in brain injury surgery is surgical site infection (SSI). Although craniotomy include into clean surgery (SSI risk is relatively low, ie 0.8 to 5.1%), but morbidity and mortality remain high due to the SSI (Kanji & Devlin 2008). SSI organs associated with increased length of stay (LOS) and higher maintenance costs when compared with the SSI superficial and SSI deep.

Clean surgery performed in an emergency can increase the risk of the SSI into 1.3 to 10.1% (Kanji & Devlin 2008). It is associated with an increased probability of risk factors associated with SSI intrinsic and extrinsic factor (Erman et al 2005, Britt et al 2007, Anderson et al 2008). Therefore, prophylactic antibiotics necessary in clean surgery brain injury patients to prevent SSI (Barker 2007, Kanji & Devlin 2008).

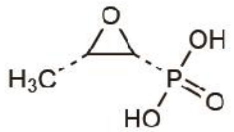

Figure 1. Chemical Structure of Fosfomycin (Sweetman 2009).

Fosfomycin has a spectrum of activity against *Staphylococcus aureus* and Staphylococcus epidermidis (Rodríguez et al 1985, Gatermann et al 1989, Sweetman 2009). Bacteria maps and antimicrobial sensitivity patterns RSUS Dr. Soetomo period January to June 2010 showed that fosfomycin against *Staphylococcus aureus* has a sensitivity of 89.5% and against Staphylococcus coagulase negative amounted to 62.5%. Fosfomycin works by inhibiting the cytoplasm enzyme uridine diphosphate-Nacetylglucosamine (UDP-GlcNAc) enolpyruvyl transferase (MurA) so that inhibiting the early stages of bacterial cell wall synthesis (intracellular). Most of the fosfomycin molecule composer groups is hydrophilic, include: epoxy, phosphate, and hydroxyl. Although fosfomycin is hydrophilic, fosfomycin has a small molecular size (138 Da) and drug binding with plasma proteins is low (2.16%). This caused fosfomycin has a relatively high penetration into the CSF (without inflammatory conditions 9-27%) (Katzung et al 2009, Patrick 2009, Sweetman 2009, Nau et al 2010). This study was a prospective observational study aimed to analyze the effectiveness of fosfomycin to prevent surgical site infections in patients with closed brain injury after craniotomy in IRD Dr. Soetomo hospital with SSI event parameters (either superficial, deep, or organ).

MATERIALS AND METHODS

This study is a prospective observational study to observe the development of surgical site condition of 30 closed brain injury patients who have undergone craniotomy. Studies conducted in the Emergency Room (IRD), F operating room, also neurosurgery department of Dr. Soetomo. Inclusion criteria for this study were: patients with a diagnosis of closed brain injury (brain injury mild, moderate, or severe), underwent craniotomy surgery without implant placement, and got a dose of prophylactic antibiotics fosfomycin 2 x 2 g iv drip for 30-60 minutes (repetition of the dose when the operation is performed > 4 hours or bleeding volume 1500 mL). This study has been approved/conduct ethical clearance by the Health Research Ethics Committee of Dr. Soetomo hospital over tested research methods (Ethical Eligibility No.159/Panke. KKE/VII/ 2012) dated July 10, 2012.

Closed brain injury patients in IRD Dr. Soetomo hospital who comply the inclusion criteria were evaluated their surgical site [includes clinical conditions (temperature, inflammation), radiological (X-rays, or CT scan), or microbiological (culture results and antibiotic sensitivity test)] for 30 days after the craniotomy. SSI diagnosis performed by surgeons or physicians, which includes: superficial SSI (involving layers of skin and subcutaneous tissue), deep SSI (involving aponeurotica, Loose connective tissue, and pericranium), SSI organs (involving skull and deeper organ) the type of the SSI criteria according to the National nosocomial Infections Surveillance (NNIS) Systems and SSI-type specific criteria according to the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN). The recorded data were patient's demographic data, surgical conditions, prophylactic antibiotics usage data, the use of other antibiotics, and evaluation of the surgical site. The obtained data then processed into tables and diagrams form.

RESULTS

During the study period (August 2012 to January 2013) obtained 36 patients who suitable with the inclusion criteria. A total of 6 patients dropped out (4 patients died without undergoing surgical site infection prior to 30 days after craniotomy surgery and 2 patients withdrew from the study because choosing outpatient health authority that closer to patients' home so the development of the site surgery cannot be followed). Patients who dropped out were not included in the analysis. Therefore, the total number of samples in this study was 30 patients.

Based on gender classification, we obtained 19 male and 11 female, male dominate by 63% compared to 37% female patients. The age distribution of patients between 11-76 years (29.2), the most was range of 18-64 years (57%). The most brain injury type was moderate brain injury with 17 patients (57%), while mild brain injury patients was 8 patients (26%), and patients with severe brain injury was the smallest type of brain injury with 5 patients (17%) (Table 1).

There was one patient experienced SSI (3,3%). SSI that happening was subdural abscess (including SSI organs) (Figure 2).

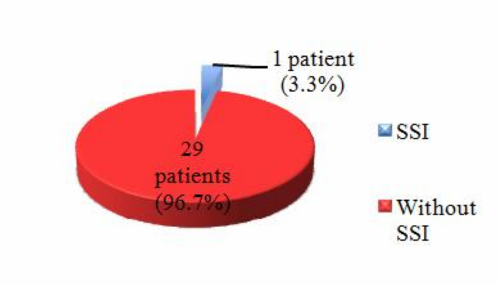

Figure 2. Evaluation of Patient's Site Surgical Development

SSI occurred in patient that received fosfomycin with duration of 1 day (figure 3).

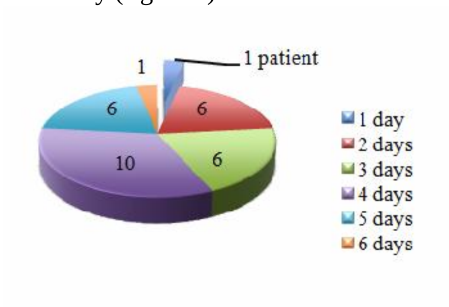

Figure 3. Fosfomycin Usage Duration & SSI Incident

Table 2 showed presurgical (related with patient) and perisurgical (related with surgical procedure) patient's risk factor (related to patient).

Table 3 contains number of risk factors per patient data associated with the occurrence of the ILO. There were 4 patients (13%) with no risk factors. While most risk factors, namely the number 5 risk factors contained in 1 patient (3%). Twenty other patients have varying risk factors, namely the 15 patients (50%) with 1 risk factor, 5 patients (17%) with 2 risk factors, and 5 patients (17%) with 3 risk factors. Surgical site infection (ILO) only occurred in patients with the highest risk factors. These five risk factors is as listed in Table 3.

Table 4 contains microbiological data, include ILO-causing bacteria and antibiotic sensitivity profile. Culture performed on day 21 days post surgery.

Table 1. Patients' characteristics based on age, sex, and brain injury

Demographic Data	Patient Number (n=30)	Percentage (%)
Gender		
Male	19	63
Female	11	37
Age		
< 18 years	12	40
18-64 years	17	57
≥ 65 years	1	3
Brain Injury Type		
Mild	8	26
Moderate	17	57
Severe	5	17

Table 2. Patients' intrinsic/preoperative and extrinsic/perioperative risk factors

Risk Factor Data	Patient (n=30)	Note
Presurgical Risk Factor		
Obesitas (BMI ≥ 30)		Obesity patients require increased prophylactic antibiotic dose
BMI < 30	30	
BMI ≥ 30	0	
Smoking history 30 days presurgical		Smoking can block wound healing process, so smoking should be stopped 30 days before operation
Smoking	4	
Didn't smoking	26	
Perisurgical Risk Factor		
Immunosupresant Drug		Immunosuppressant administration in perioperative period should be avoided (if possible)
Use	6	
Didn't use	24	
Surgical Characteristic		Operation in emergency condition increases the risk of ILO
Cito/emergency (≤ 4 hours from admission hour)	22	
Urgent (4-24 hours from admission hour)	7	
Electif (> 24 jam hours from admission hour)	1	
Fosfomycin Usage Duration		Prophylactic antibiotic can be provided maximally 24 hours after operation
1 Day	1	

> 1 day	29	
Surgical Duration		Craniotomy > 3.75 hours increases the risk of ILO
≤ 3,75 hours	16	
> 3,75hours	14	
Bleeding Volume (mL)		Prophylactic antibiotic administration is suggested if bleeding occurs in a volume of ≥ 1500 mL
< 1500 mL	27	
≥ 1500 mL	3	
Drainase Installation Duration		Drainase Installation > 5 5 days increase SSI risk factor
≤ 5 days	30	
> 5 days	0	
ICP monitor Installation Duration		ICP monitor Installation > 5 days increase SSI risk factor
≤ 5 days	2	
> 5 days	0	

Tabel 3. Total patients' risk factors and ILO incidence

Risk factor numbers(*)	Patient (n=30)	ILO incidence
No risk factor	4	0
1	15	0
2	4	0
3	6	0
4	0	0
5	1	1 (3.3%)

Note: The risk factors intended include: smoking history 30 days preoperatively, use of immunosuppressants, undergoing cito/ emergency operation, duration of operation > 3.75 hours, and bleeding volume of ≥ 15 mL. (*) total risk factors 2 indicate that the patients have 2 out of 5 ILO risk factors, for example: undergoing cito/emergency operation and duration of operation > 3.75 hours.

Tabel 4. Microbiological data on ILO-causing bacteria and antibiotic sensitivity profiles

Data	Hasil
Material	Pus from operation wound
Bacteria	*Pseudomonas aeruginosa*
Antibiotic sensitivity profile	
Sensitive	Fosfomisin
	Piperacillin tazobactam
	Meropenem
Intermediate	Aztreonam
Resistant	Amikacin
	Gentamycin
	Tobramycin
	Ceftazidim
	Ciprofloxacin
	Levofloxacin
	Ticarcillin-Clavulanic Acid

Table 5. Data on Length of Stay (LOS)

LOS Data	Brain Injury Type	MRS 1	MRS 2	Total
Without SSI	Mild	4-11 days	-	4-11 days
	Moderate	6-26 days	-	6-26 days
	Severe	8-31 days	-	8-31 days
SSI	Mild	6 days	27 days	33 days

Note: MRS1 is hospitalization due to brain injury that lead the patient to undergo craniotomy. MRS2 was hospitalization due to ILO experienced by the patients that lead them to undergo operation for abscess excision and forehead flap.

The patient's condition when diagnosed SSI, namely: normal WBC (7,68.103 μ/L), normal temperature (37.1 °C), dizziness, GCS 456, the site open and pus on surgical site, and the results of the CT scan which indicate the presence of a mass in the subdural area. The patient subsequently underwent inpatient with empiric therapy ceftriaxon 2 x 1g (iv) and metronidazole 3 x 500 mg (iv) for 6 days. Culture results came out on day 7 with bacteria and sensitivity (table 4), so 3 x 1g meropenem as an antibiotic definitive was given. Meropenem was given for 9 days. Patients undergoing surgery exciseon abscess and fore head flap on day 13. Improved patient outcomes after therapy with normal WBC (7,31.103 μ/L), normal temperature (36.5 °C), reduced complaints of dizziness, GCS 456, and the condition of the surgical site without open site and pus were negative.

LOS distribution in patients without SSI was 4-31 days (11 days). In patients without SSI, patient's LOS severe brain injury > moderate brain injury > mild brain injury. While LOS in patients with SSI were 33 days (6 days at the time of the first MRS and 27 days during the second MRS). LOS patients with SSI 3x longer LOS than patients without SSI (with the same diagnosis, ie mild brain injury) (Table 5).

DISCUSSION

From the results of the evaluation of the surgical site samples of 30 patients during 30 days showed that the SSI events occurred in 1 patient (3.3%). The aim of prophylactic antibiotics usage was to prevent the SSI (Bratzler et al 2013). Antibiotic prophylaxis was effective when it can prevent surgical site infections to < 5% in Patients who experienced a clean surgical (craniotomy). Other studies have also shown that antibiotic prophylaxis in craniotomy prevent the SSI effectively even in patients with low risk, which can lower the SSI from 10.0% to 4.6% ($p < 0.0001$) (Korinek et al 2005). Therefore, the percentage incidence of SSI obtained 3.3% in this study, showed that Fosfomycin prevent surgical site infections effectively in patient with closed brain injury after craniotomy in IRD Dr. Soetomo hospital.

There were 4 patients with a smoking history prior to surgery in this study, and one of them suffered SSI. Nicotine contained in cigarettes, can delay site healing and increase the risk of the SSI (Mangram et al 1999). Smoking can decrease blood circulation to the skin through microvascular obstruction of platelet aggregation and increase hemoglobin that was not functioning properly. Therefore, stop smoking 30 days before surgery is recommended (level A II) in an effort to prevent the occurrence of the SSI (Anderson et al 2008).

In this study, there were 6 patients receiving immune-suppressant drugs (dexamethason) and one of them suffered the SSI. Dexamethason with a dose of 4 mg administered as therapy to cope with allergic reactions (pruritus, urticaria) due to PRC transfusion while being treated at the IRD and Surgical Irna F. Chemotherapy or other immunosuppressant drugs can suppress the immune system. Steroids or other immunosuppressant drugs given in the perioperative period predisposes to the SSI. SSI occurred significantly more frequently in patients who received preoperative steroids (12.5%) than those without steroids (6.7%). However, in another study states that there is no relationship between the use of steroids with risk ILO (Mangram et al 1999). Therefore, if possible, immunosuppressant drugs should not be given in the perioperative period (recommendation level C II) (Anderson et al 2008).

Looking from the surgical characteristic, there were 22 patients who underwent emergency surgery in this study and one of them suffered SSI. Clean surgical performed in an emergency can increase the risk of the SSI into 1.3 to 10.1%. It is associated with an increased likelihood of risk factors associated with the SSI (Kanji & Devlin 2008). On clean surgical with emergency conditions (21.05%) was significantly higher than the SSI on elective surgery (7.61%) ($p = 0.002$) (Mahesh et al 2010). Risk factors for infection were higher in all categories, both preoperative and perioperative if surgery was performed in an emergency (emergency).

In this study, there were 14 patients who underwent surgery with a duration of > 3.75 hours, and one of them suffered the SSI. Cut points for the duration of the operation were the 75th percentile of the distribution of the duration of the operation of national NHSN database. Duration of surgery higher than the cut-point lead to a higher risk. According to the NHSN report in 2009, the cut point for craniotomy was 225 minutes (3.75 hours). Duration of surgery> cut point is one component of NHSN risk index. The average incidence of SSI on clean surgical increased significantly with increasing duration of surgery ($p = 0.018$) (Mahesh et al 2010). Other SSI risk factors were including obesity and cutting hair (bald). In this study, no patients were obese. Obesity was defined by a BMI ≥ 30 kg/m2, was one of the risk factors of the SSI (Mangram et al 1999). Increasing the dose antibiotic prophylaxis was recommended (level A II) in obese patients (Anderson et al 2008).

Culture performed on day 21 of post surgery days with pus material from the surgical site. Bacteria found was *Pseudomonas aeruginosa*. Prospective study on 418 patients who followed their operation site, showed that *Pseudomonas aeruginosa* (26%) is the second most bacteria SSI after *Staphylococcus aureus* (34%) (Mahesh et al 2010). Study in neurosurgical showed that *Pseudomonas aeruginosa* was one of the causes of the SSI (10%). Prospective observational study in Kuala Lumpur on 30 patients with post-craniotomy SSI showed that *Staphylococcus aureus* (36%), MRSA (17%), *Pseudomonas aeruginosa* was the causes of the SSI (13%).

Subdural abscess SSI that occurred in this study led to high LOS on SSI patient. In patients without SSI, the LOS of patients severe brain injury (8-31 days) > moderate brain injury (6-26 days) > mild brain injury (4-11 days). While LOS in patients with SSI (mild brain injury) of 33 days (6 days at the time of the first MRS and 27 days during the second MRS). LOS patients with SSI 3x longer LOS than patients without SSI (with the same diagnosis, ie mild brain injury). The first MRS was the MRS brain injury so patients underwent craniotomy surgery, while second MRS was due SSI so patients undergoing surgery excise abscess and fore head flap. When compared with the superficial SSI and deep SSI, organs SSI associated with increased LOS and higher maintenance costs. Retrospective study of 103 patients post craniotomy showed that LOS in patients with SSI (an average of 58 days with a range of 10-154 days) was significantly higher than LOS patients without SSI (average of 15 days with a range of 2-76 days ($p < 0.001$) (Cha et al 2010). Systematic review of 3 studies on the relationship between the SSI with LOS, showed an increase in LOS (post-surgery) for 5-18 days.

Based on the bacteria map and antimicrobial susceptibility in Dr. Soetomo hospital period January-June 2010 fosfomycin have known that a relatively high sensitivity, good against *Staphylococcus aureus* (89.5%), as well as against Staphylococcus coagulase negative (62.5%). When compared with bacteria map and antimicrobial susceptibility in Dr. Soetomo hospital period from July to December 2012 at Surgery Ward, can be seen a decrease in the sensitivity of fosfomycin against *Staphylococcus aureus* (60%) against *Staphylococcus coagulase* negative and (12%). This shows the changing patterns of antimicrobial susceptibility in Dr. Soetomo hospital can be caused due to the use of fosfomycin as prophylactic antibiotics.

Antibiotic prophylaxis recommended by Kanji & Devlin (2008) was sefazolin or cefotaxime 1g 1 x 1 x 1 g, or trimethoprim-sulfamethoxazol 1 x 160/800 mg iv when patients with penicillin allergy (level IA) with the possibility of SSI causing pathogens are *Staphylococcus aureus* and *Staphylococcus epidermidis*. Antibiotic Prophylaxis in Surgery 2012 recommended sefazolin as antibiotic prophylaxis in clean neurosurgical with the same pathogen causes the SSI. For patients who were allergic to penicillin, clindamycin was recommended. Sefazolin also recommended as antibiotic prophylaxis in clean neurosurgical with alternative antibiotics clindamycin or vancomycin in patients allergic to β-lactams. Restricted vancomycin occurred only in patients with MRSA colonization (levels I- III/A) (Kanji & Devlin 2008, Bratzler et al 2013). Based on the guidelines above, it can be seen that the recommended antibiotic prophylaxis in clean neurosurgical operations were sefazolin, cefotaxime, or if the patient is allergic to penicillin can be used sulfamethoxazol-trimethoprim, clindamycin, or vancomycin. However, preparations of clindamycin and trimethoprim-sulfamethoxazol by administering parenteral route was not available in Indonesia. While the usage of vancomycin was restricted only in patients with MRSA colonization.

Penetration of antibiotics into the CSF depends on the characteristic of their pharmacokinetic. Central nervous compartment surrounded by at least one layer of cells consisting of two membrane lipids mostly bound form tight junctions) so that the overall CNS seen surrounded by a lipid layer. Therefore, the lipophilicity of the compounds increase its penetration into the CNS membranes. Based on molecular structure, sefazolin and cefotaxime were lipophilic, while the fosfomycin was hydrophilic. The antibiotic lipophilicity looked from the group that composes the molecule. Most of the constituent groups of sefazolin were lipophilic molecules, namely: methyl, thiometil, thiadiazol, tetrazol-1 -ylacetamido, and cephem. Hydrophilic group only carboxylic. Most of the constituent groups of cefotaxime were also lipophilic molecules, namely: asetoksimetil, aminothiazol, methoxyimino acetamido and cephem. Hydrophilic group was only carboxylic. While on fosfomycin, most of the molecule wa hydrophilic constituent groups, include: epoxy, phosphate, and hydroxyl. Although fosfomycin was hydrophilic, fosfomycin has a small molecular size and binding of drugs to plasma proteins was low. This leads to fosfomycin has a relatively high penetration into the CSF. The entry of the compound into the CSF is inversely proportional to the square root of the molecular mass. The smaller the mass of the molecule, compound penetration into the CSF is easier (Nau et al 2010). Fosfomycin has a smaller molecular mass (138 Da), when compared with sefazolin (450 Da) and cefotaxime (455 Da). Ties of drugs to plasma proteins (mainly albumin or globulin) resulting in low drug penetration into the CSF. Fosfomycin bonds with plasma proteins (2.16%) lower than sefazolin (85%) and cefotaxime (40%). t ½ sefazolin equal to fosfomycin, which was 1.8 hours, while the cefotaxime was shorter, 1.5 hours. Sefazolin and cefotaxime is a weak acid with a pH that is almost the same, sefazolin 4.0-6.0; cefotaxime 4.5-6.5, whereas fosfomycin is a weak base with a pH of 6.5 to 8.5. With the above pharmaco-kinetics, causing CSF penetration of fosfomycin (without inflammatory conditions 9-27%) higher than sefazolin (inflammatory conditions 1-4%) and cefotaxime (at the 12% condition without inflammation, the inflammatory condition of 4-17%) (Katzung et al 2009, Patrick 2009, Sweetman 2009, Nau et al 2010). However, the usage of antibiotic fosfomycin was restricted in Dr. Soetomo hospital. Thus as an alternative to craniotomy prophylaxis in patients with closed brain injury can conducted study using prophylactic antibiotics such on guidelines of prophylactic antibiotics, such as cefotaxime.

CONCLUSION

Fosfomycin effectively prevent surgical site infection (SSI) in patients with closed brain injury after craniotomy in IRD Dr. Soetomo hospital with SSI percentage of 3.3%. SSI-causing bacteria are *Pseudomonas aeruginosa*. Antibiotics that sensitive against to bacteriaare fosfomycin, Piperacillin tazobactam, and meropenem. LOS of patients with SSI 3x longer than without SSI.

REFERENCES

Anderson DJ, Kaye KS, Classen D, Arias KM, Podgorny K, Burstin H, Calfee DP, Coffin SE, Dubberke ER, Fraser V, Gerding DN, Griffin FA, Gross P, Klompas M, Lo E, Marschall J, Mermel LA, Nicolle L, Pegues DA, Perl TM, Saint S, Salgado CD, Weinstein RA, Wise R, Yokoe DS (2008). Strategies to prevent surgical site infections in acute care hospitals. Infect Control Hosp Epidemiol 29, S51-S61

Barker FG (2007). Efficacy of prophylactic antibiotics against meningitis after craniotomy: a meta-analysis. Neurosurgery 60, 887-894

Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA

(2013). Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 70, 195-283

Britt LD, Trunkey DD, Feliciano DV (2007). Acute Care Surgery Principles and Practice, New York, Springer-Verlag, p 315-347

Cha KS, Cho OH, Yoo SY (2010). Risk factors for surgical site infections in patients undergoing craniotomy. J Korean Acad Nurs 40, 298-305

Erman T, Demirhindi H, Göçer AI, Tuna M, Ildan F, Boyar B (2005). Risk factors for surgical site infections in neurosurgery patients with antibiotic prophylaxis. Surg Neurol 63, 107-112

Gatermann S, Schulz E, Marre R (1989). The microbiological efficacy of the combination of fosfomycin and vancomycin against clinically relevant staphylococci. Infection 17, 35-37

Kanji S and Devlin JW (2008). Antimicrobial prophylaxis in surgery. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM (eds). Pharmacotherapy A Pathophisiologic Approach, 7th ed. New York, The McGraw- Hill Co. Inc, p 2027-2040

Katzung BG, Masters SB, Trevor AJ (2009). Basic and Clinical Pharmacology, 11th ed., New York, The McGraw–Hill Companies Inc

Korinek AM, Golmard JL, Elcheick A, Bismuth R, van Effenterre R, Coriat P, Puybasset L (2005). Risk factors for neurosurgical site infections after craniotomy: a critical reappraisal of antibiotic prophylaxis on 4,578 patients. Br J Neurosurg 19, 155-162

Mahesh CB, Shivakumar S, Suresh BS, Chidanand SP, Vishwanath Y (2010). A prospective study of surgical site infections in a teaching hospital. Journal of Clinical and Diagnostic Research 4, 3114-3119

Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR (1999). Guideline for prevention of surgical site infection, 1999. Hospital infection control practices advisory committee. Infect Control Hosp Epidemiol 20, 250-278

Nau R, Sörgel F, Eiffert H (2010). Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev 23, 858-883

Patrick GL (2009). An Introduction to Medicinal Chemistry, 4th ed., New York, Oxford University Press

Rodríguez A, Vicente MV, Olay T (1985). Comparison of fosfomycin and vancomycin therapy for experimental endocarditis due to methicillin-resistant Staphylococcus epidermidis. Eur J Clin Microbiol 4, 603-605

Sweetman S (2009). Martindale: the complete drug references, 36th ed., London, Pharmaceutical Press, p 278-279

Wahyuadi J, Suryaningtyas W, Susilo RI (2007). Pedoman Tatalaksana Cedera Otak (Guideline for Management of Traumatic Brain Injury), Surabaya, Tim Neurotrauma RSU Dr Soetomo Fakultas Kedokteran Universitas Airlangga

Wahyuhadi J (2010). Laporan Pelayanan SMF Bedah Saraf RSUD Dr. Soetomo Juni 2010, Surabaya, RSU Dr Soetomo

Laporan Pelayanan SMF Mikrobiologi Klinik RSUD Dr. Soetomo Juni 2010, Surabaya, RSU Dr Soetomo