



The Relationship Of Anti-Inflammation Non Steroid Use Patterns With Side Effects In Patients Post Appendectomy At Jemursari Islamic Hospital

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ABSTRACT

Background: Appendicitis is a condition where there is acute inflammation of the vermiform appendix which causes patients to undergo surgery frequently. NSAIDs are given to patients after appendectomy surgery to relieve pain. Inappropriate pattern of NSAID use can cause drug side effects.

Objective: This study aims to analyze the relationship between the pattern of use of non steroidal anti-inflammatory analgesics and drug side effects in post-appendectomy patients at Jemursari Hospital Surabaya in 2019-2020.

Methods: This type of research is descriptive analytic with a cross sectional design. This study used 62 samples medical record of post-appendectomy patients in 2019-2020 who were given NSAID therapy. Chi-Square Test and Fisher's Exact Test ($p < 0.05$) was used to analyze the relationship between NSAID use patterns and side effects.

Results: There was a relationship between the type of drug Mafenamic Acid 500mg with nausea, Ketorolac 30mg with hypotension, Ketorolac 90mg with dizziness, and Santagesic 500mg with dyspepsia ($p < 0.05$). Administration of therapy with less dose was associated with hypotension ($p < 0.05$). The duration of therapy for 4 days was associated with nausea, vomiting and duration of therapy for 5 days was associated with constipation and dyspepsia.

Conclusion: The use of drugs (type of drug, accuracy of dose and duration of therapy) of NSAIDs in post-appendectomy patients is associated with drug side effects.

Introduction

Appendicitis is a condition where there is acute inflammation of the vermiform appendix caused by bacterial infection, tumors of the appendix, and worms which can cause blockages to form in the lumen (Diantari *et al.*, 2018). The presence of these blockages can cause more mucus production and a decrease in the elasticity

of the appendix wall and a feeling of pain occurs (Flum, 2015).

In Indonesia, appendicitis patients account for around 27% of the population (Kemenkes, 2018). In 2017 in East Java, there were 5,980 cases of appendicitis and 177 of them died (Dinkes Jatim, 2017). Appendicitis can cause complications if left unchecked and can lead to perforation of the

appendix if not treated immediately. The most appropriate action to treat appendicitis is an appendectomy (Sjamsuhidajat, 2016). Appendectomy is a surgical procedure or surgical removal of the appendix by opening the abdomen. Almost all patients feel pain after surgery (Zulfikar *et al.*, 2015).

The analgesic used in post appendectomy patients is to use non-steroidal anti-inflammatory drugs (NSAIDs) (Baumann and Strickland, 2014). Inadequate pain management in post-appendectomy patients can have side effects (drug related problems) in patients (Handayani *et al.*, 2019).

Drug Related Problems (DRP) are unwanted events experienced by the patient concerned that are related to drug therapy, this can disturb achievement of therapeutic goals. According to Michele's research (2015) DRP is a case that can cause patient mortality and morbidity.

Methods

This type of research is descriptive analytic with cross-sectional design. The population of this study were all post-appendectomy patients who received post operative analgesic therapy in 2019-2020 as many as 143 and the sample used was 62 research subjects. The sampling technique uses the technique non-random sampling by taking samples purposive sampling.

Univariate data analysis used a frequency distribution with a percentage size for categorical data and numerical data used the mean or average value. Bivariate data analysis using Chi-Square or Fisher's exact test with a significance level of 5% ($P < 0.05$).

Results and Discussion

Pattern of use of NSAID group analgesics in post-appendectomy patients

a. Drug type

Table 1. Characteristics of NSAID drug types

No	Drug Type & dose (mg)	Frequency	Percentage
1	Mefenamic Acid 500 mg	4	6,40
2	Ketorolac 30 mg	36	58,06
3	Ketorolac 90 mg	6	9,67
4	Antrain 500 mg	6	9,67
5	Santagasic 500 mg	2	3,22
6	Santagasic 1000 mg	4	6,40
7	Ibuprofen 30 mg	3	4,83
8	Ibuprofen 90 mg	1	1,61
Total		62	100,00

Based on Table 1, it can be obtained that most of the respondents (58.06) used the type of drug Ketorolac 30 mg. The choice of the type of drug Ketorolac 30mg is widely used because it is similar to the drug morphine, but Ketorolac does not cause side effects on the central nervous system. This study is in accordance with Darajatun *et al.*, (2017) that Ketorolac is effective as a

substitute for morphine in post surgical patients.

b. Drug dose

Table 2. Accuracy of NSAID Dosage

No	Accuracy of Doses	Frequency	Percentage
1	Less doses	6	9,67
2	Therapeutic doses	51	82,25
3	More doses	5	8,06
Total		62	100,00

Based on Table 2, information can be obtained that in general (82.25%) of respondents received NSAID doses according to the therapeutic doses. This research agrees with the research conducted by Ramadani *et al.*, (2011) that the administration of NSAID therapy according to the therapeutic doses effects to recovery of post operative patients.

c. Length of therapy

Table 3. Duration of NSAID Therapy

No	Long Therapy	Frequency	Percentage
1	1 day	2	3,22
2	2 days	6	9,67
3	3 days	45	72,58
4	4 days	7	11,29
5	5 days	2	3,22
Total		62	100,00

Based on Table 3, information was obtained that most of the respondents (72.58%) received NSAID therapy for 3 days.

Administering a therapeutic dose for 3 days is the minimum duration of therapy that can relieve pain in postoperative patients. Using drugs for a long time or too fast can interfere with the mechanism of

action of the drug so that it can cause side effects (Tejovathin *et al.*, 2017).

Side effects of using NSAIDs in the patients post appendectomy

Table 4. Number of Respondents

Experiencing of NSAIDs's Side Effects

No	Side Effects	Frequency	Percentage
1	Yes	44	71,00
2	No	18	29,00
Total		62	100,00

Based on Table 4 most (71.00%) respondents experienced side effects of NSAID.

Table 5. Description of the side effects of NSAIDs

No	Side Effects	Frequency	Percentage
1	Itchy	2	3,33
2	Headache	9	15,00
3	Nausea	21	35,00
4	Vomiting	3	5,00
5	Diarrhea	0	0,00
6	Constipation	2	3,33
7	Hypotension	6	10,00
8	Hypertension	13	21,66
9	Dyspepsia	4	6,66
Total		60	100,00

Based on Table 5, almost half (35.00%) of the respondents who received NSAIDs experienced the side effect of nausea. Most patients experience side effects after NSAID therapy because the drug works by inhibiting prostaglandins (Kumar *et al.*, 2018).

The relationship between NSAID use patterns and drug side effects (drug related problems) in the patients post appendectomy

Table 6. The relationship of NSAID Drug Types with Drug Side Effects (Drug Related Problems)

<i>Chi-Square Test, Fisher's Exact Test (p<0.05)</i>									
Drug Type	Itchy	Head ache	Nausea	Vomiting	Diarrhea	Constipation	Hypotension	Hypertension	Dyspepsia
Mefenamic Acid 500 mg	0,87	0,52	0,01	0,18	0,00	0,87	0,65	0,38	0,76
Ketorolac 30 mg	0,35	0,12	0,57	0,07	0,00	0,18	0,005	0,12	0,21
Ketorolac 90 mg	0,81	0,003	0,67	0,73	0,00	0,81	0,52	0,10	0,65
Antrain 500 mg	0,81	0,62	0,67	0,73	0,00	0,18	0,09	0,22	0,34
Santagesic 500 mg	0,93	0,72	0,43	0,90	0,00	0,06	0,18	0,62	0,03
Santagesic 1000 mg	0,84	0,55	0,44	0,22	0,00	0,84	0,06	0,28	0,70
Ibuprofen 30 mg	0,90	0,61	0,28	0,14	0,00	0,90	0,73	0,10	0,81
Ibuprofen 90 mg	0,96	0,85	0,66	0,95	0,00	0,96	0,90	0,21	0,93

*Description: Numbers with bold is significant (p<0.05)

Table 7. The relationship of NSAID Drug Doses with Drug Side Effects (Drug Related Problems)

<i>Chi-Square Test, Fisher's Exact Test (p<0.05)</i>									
Drug Doses	Itchy	Head ache	Nausea	Vomiting	Diarrhea	Constipation	Hypotension	Hypertension	Dyspepsia
Less doses	0,81	0,62	0,32	0,73	0,00	0,18	0,009	0,22	0,34
Therapeutic doses	0,67	0,19	0,19	0,55	0,00	0,32	0,06	0,58	0,55
More doses	0,84	0,14	0,44	0,77	0,00	0,84	0,59	0,28	0,70

*Description: Numbers with bold is significant (p<0.05)

Table 8 The relationship between NSAID therapy duration and drug side effects

<i>Chi-Square Test, Fisher's Exact Test (p<0.05)</i>									
Long Therapy	Itchy	Head ache	Nausea	Vomiting	Diarrhea	Constipation	Hypotension	Hypertension	Dyspepsia
1 day	0,93	0,27	0,56	0,90	0,00	0,93	0,81	0,37	0,87
2 days	0,81	0,37	0,07	0,73	0,00	0,81	0,52	0,10	0,65
3 days	0,52	0,22	0,32	0,18	0,00	0,07	0,13	0,25	0,30
4 days	0,78	0,31	0,03	0,03	0,00	0,78	0,47	0,17	0,61
5 days	0,93	0,72	0,56	0,90	0,00	0,002	0,81	0,62	0,03

*Description: Numbers with bold is significant (p<0.05)

Based on Table 6, it is informed that the types of drugs associated with side effects is:

- a. Mafenamic Acid 500mg related with side effects of nausea ($p < 0.05$) and has a weak correlation value of 0.343 or < 0.5 in the *Cramer's V test*.
- b. Ketorolac 30 mg is associated with side effects of hypotension ($p < 0.05$) and has a weak correlation value of 0.389 or < 0.5 in the *Cramer's V test*.
- c. Ketorolac 90 mg is associated with side effects of headache ($p < 0.05$) and has a weak correlation value of 0.429 or < 0.5 in the *Cramer's V test*.
- d. Santagesic 500 mg is associated with side effects of dyspepsia ($p < 0.05$) and has a weak correlation value of 0.400 or < 0.5 in the *Cramer's V test*.

Based on Table 7, it is informed that the use of NSAIDs at less doses is associated with side effects of hypotension ($p < 0.05$) and the value of strong relationship is 0.598 or > 0.5 on the *Cramer's V test*.

Based on Table 8, it is informed that the types of drugs associated with side effects are:

- a. The duration of 4 days of therapy is associated with side effects of nausea ($p < 0.05$) and has a weak correlation value of 0.325 or < 0.5 in the *Cramer's V test*.

- b. The duration of 4 days of therapy is associated with side effects of vomiting ($p < 0.05$) and has a weak correlation value of 0.395 or < 0.5 in the *Cramer's V test*.
- c. The duration of 5 days of therapy is associated with side effects of constipation ($p < 0.05$) and has a strong correlation value of 0.701 or > 0.5 in the *Cramer's V test*.
- d. The duration of therapy of 5 days is associated with side effects of dyspepsia ($p < 0.05$) and has a strong correlation value of 0.558 or > 0.5 in the *Cramer's V test*.

Non-opioid analgesics widely used in post-appendectomy patients are non-steroidal anti-inflammatory drugs (NSAIDs) and can cause side effects in their use. Drug side effects are unwanted events that occur in patients related to drug therapy (Luke *et al.*, 2017). Using analgesics non-opioid (NSAIDs) that are widely used in post-appendectomy patients are NSAIDs which work to prevent the formation of prostaglandins in response to impulses thereby reducing the number of pain impulses received by the CNS. NSAIDs are lipophilic and acidic, so they can cause damage topically, while the systemic effects of NSAIDs are caused by mucosal damage that occurs due to decreased prostaglandin production. Decreased production of prostaglandins can also cause damage to the

stomach and duodenum (Baumann & Strickland, 2014).

In this study the types of drugs associated with side effects were the use of Mefenamic Acid 500 mg with side effects of nausea, Ketorolac 30 mg with side effects of hypotension, Ketorolac 90 mg with side effects of headache, Santagesic 500 mg with side effects of dyspepsia and had a weak relationship strength (<0.5). The administration of Mefenamic Acid 500 mg, Ketorolac 30 mg, Ketorolac 90 mg and Santagesic 500 mg therapy causes side effects with weak relationship because basically every administration of therapy will always cause unexpected side effects. All drugs in this class is NSAID drugs that work by inhibiting prostaglandins and COX inhibitors.

Mefenamic acid is a class of NSAID drugs that are COX non-selectively that works to inhibit pain stimuli in organs that secrete cyclooxygenase enzymes (Kresnadi & Mulyo, 2016). The dosage for using Mefenamic Acid is 250 mg – 500 mg with a maximum dose of 1500 mg per day (Catamara, 2016). This drug has side effects on the gastrointestinal tract such as nausea, vomiting, dyspepsia, diarrhea to bloody diarrhea, and other symptoms of irritation to the gastric mucosa (Gunawan, 2016). This study agrees with research conducted by Amrullah and Utami (2016), and Idacahyatiet al., (2019) that the use of

Mefenamic Acid at a dose of 250mg-500mg causes the most side effects, namely nausea. Nausea caused by Mefenamic Acid works as COX inhibitors which can inhibit prostaglandin synthesis, if prostaglandin production decreases it will cause clinical symptoms such as nausea, vomiting and even stomach damage (Kang, 2011).

Ketorolac is a carboxylic acid pyrrolizine class of drugs which has a moderate anti-inflammatory effect and is a potent analgesic for pain relief. Ketorolac exerts an anti-inflammatory effect by inhibiting COX-1 and inhibiting granulocyte attachment to damaged blood vessels, stabilizing lysosomal membranes and inhibiting migration leukocytes to the site of inflammation (Kumar et al., 2018). In this study Ketorolac at a dose of 30 mg was associated with hypotension, whereas a dose of 90 mg was associated with headache. Ketorolac often causes disturbances in lowering blood pressure and headache, but the exact mechanism is not known (Kang, 2011). Decreased production of prostaglandins (PGE1 and PGE2) is believed to be one of the mechanisms by which these side effects occur (Landefeld et al., 2016).

Santagesic is one of the anti-inflammatory drugs inflammation non-steroids (NSAIDs) they contain metamizole, this drug works by inhibiting the synthesis of prostaglandins in the

peripheral and central nervous systems (Gunawan, 2016). This study agrees with previous research by Ida cahyati *et al.*, (2019) that the use of NSAIDs such as Santagesic often causes dyspeptic side effects. The mechanism of dyspepsia occurs due to inhibition of prostaglandin synthesis which causes reduced resistance of the gastric mucosa (Amrulloh & Utami, 2016).

In this study, the use of NSAIDs at low doses was associated with side effects of hypotension and had a strong relationship (>0.5). NSAIDs that use less doses are Antrain 500 mg (5 respondents) and Santagesic 500 mg (1 respondent) which are given to respondents aged 12-15 years. These side effects arise due to the inappropriate use of NSAIDs in the selection of doses. Selection of the less dose will be cause unexpected drug reactions, especially in children, because the body's response to drugs is not as good as that of adults.

The results of this study stated that the administration of NSAIDs with a duration of therapy of 4 days was associated with side effects of nausea and vomiting. While the duration of therapy of 5 days is associated with side effects of constipation and dyspepsia and has a strong relationship (>0.5). NSAIDs are prostaglandin inhibitors and COX inhibitors, so the longer the therapy is given, the stronger it will cause digestive tract disorders. This

research agrees with previous research conducted by Amrulloh & Utami, (2016) and Idacahyatiet al., (2019) that the longer the administration of NSAID therapy increases the incidence of nausea, vomiting, constipation and even dyspepsia.

Conclusion

1. The pattern of use of non-steroidal anti inflammatory analgesics in post appendectomy patients at Jemursari Surabaya Hospital in 2019-2020 is:
 - a. Most of the NSAIDs used were ketorolac 30 mg (58.1%).
 - b. The most widely used doses of NSAIDs are generally the dose according to therapy (82%).
 - c. The duration of administration of NSAIDs to most of the respondents was 3 days (72.58%).
2. The side effects of using non-steroidal anti inflammatory group analgesics in post appendectomy patients at RSI Jemursari Surabaya in 2019-2020 which caused almost half of them were nausea (33.9%).
3. Statistically, there is a relationship between patterns of NSAID use and side effects based on:
 - a. Types of NSAID drugs: Mafenamic acid 500 mg for nausea, Ketorolac 30 mg for hypotension, Ketorolac 90 mg for headache, and Santagesic

500 mg for dyspepsia and have a weak correlation value (<0.5).

- b. Dosage accuracy: The use of NSAIDs is less associated with hypotension and has a strong correlation value (>0.5)
- c. Length of therapy: 4 days associated with nausea and vomiting and has a weak correlation value (>0.5).

References

- Aleq, M. S. (2011). Apendisitis Akut: Bagaimana Seharusnya Dokter Umum Dan Perawat Dapat Mengenali Tanda Dan Gejala Lebih Dini Penyakit Ini? In *Jurnal Keperawatan*, (2)1, pp. 15-20.
- Arifuddin, A., Salmawati, L., & Prasetyo, A. (2017). Faktor Resiko Kejadian Apendisitis di Bagian Rawat Inap RSU Anutapura Palu 2017. *Jurnal Kesehatan Masyarakat*, (8)1, pp. 26–33.
- Bahrudin, M. (2018). Patofisiologi Nyeri (Pain). *Saintika Medika*, (13)1, pp. 7-13.
- Baumann & Strickland, J. M. (2014). "Chapter 44: Pain Management." *Pharmacotherapy: A Pathophysiologic Approach. 9th Ed.* McGraw-Hil.
- Blondell, R. D., Azadfard, M., & Wisniewski, A. M. (2013). Pharmacologic therapy for acute pain. *American Family Physician*, (87)11, pp. 766–772.
- Braun, E. B., Scarlett, J. A., Schwedt, T. J., & Swarm, R. A. (2010). Pain Management in the Head and Neck Patient. In *Cummings Otolaryngology - Head and Neck Surgery* (Seventh Ed). Elsevier Inc.
- Brunner, S. (2013). *keperawatan medikal-bedah (edisi 12)* (12th ed.). Jakarta: EGC, pp. 60-110.
- Catamara. (2016). Therapeutic Class Overview Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). *Pharmaceutical Journal*, (7)22, pp. 1-7.
- Chandra, C., Tjitrosantoso, H., & Lolo, W. A. (2016). Studi Penggunaan Obat Analgesik Pada Pasien Cedera Kepala (Concussion) Di Rsup Prof. Dr. R. D. Kandou Manado Periode Januari-Desember 2014. *Pharmacon*, (5)2, pp. 55-58.
- Darajatun, L. A., Alifiar, I., & Nofianti, T. (2017). Gambaran Penggunaan Analgetika Pada Pasien Pasca Bedah Di Ruang Iii Dan Melati Lantai 4 Rsud Dr. Soekardjo Kota Tasikmalaya. *FITOFARMAKA: Jurnal Ilmiah Farmasi*, (7)1, pp. 29–35.
- Diantari, D. A. W., Wiguna, I. N. A. A., & Nirvana, I. W. (2018). Gambaran evaluasi tingkat nyeri pasien pasca operasi radang usus buntu dengan bedah terbuka dan laparoskopi di Rumah Sakit Umum Pusat Sanglah Denpasar tahun

2016. *Intisari Sains Medis*, (9)2, pp. 100–106.
- Elsevier Point of Care. (2020). Apendicitis. *Elsevier*, (2)5, pp. 1–39.
- Flum, D. R. (2015). Acute appendicitis—appendectomy or the “antibiotics first” strategy. *New England Journal of Medicine*, (372)20, pp. 1937–1943.
- Gunawan, S. G. (2016). *Farmakologi dan Terapi Edisi 6*. Jakarta: Badan. Penerbit FKUI, pp. 234-251.
- Hall, J. E., & Hall, M. E. (2020). *Guyton and Hall textbook of medical physiology e-Book*. Elsevier Health Sciences.
- Handayani, D., & Dominica, D. (2019). Gambaran Drug Related Problems (DRP’s) pada Penatalaksanaan Pasien Stroke Hemoragik dan Stroke Non Hemoragik di RSUD Dr M Yunus Bengkulu. *Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia*, (5)1, pp. 36.
- Handayani, S., Arifin, H., & Manjas, M. (2019). Kajian Penggunaan Analgetik pada Pasien Pasca Bedah Fraktur di Trauma Centre RSUP M. Djamil Padang. *Jurnal Sains Farmasi & Klinis*, (6)2, pp. 113.
- Idacahyati, K., Tita, N., Geby, A & Maritsa, N. (2019). Hubungan Tingkat Kejadian Efek Samping Antiinflamasi Non Steroid dengan Usia dan Jenis Kelamin. *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia*, (6)2, pp. 56-61.
- Kementerian Kesehatan RI. (2018). Kasus Appendicitis di Indonesia. Available from <https://www.Artikelkedokteran.Com/Ar sip/Kasus-Apendisitis-Di Indonesia-Pada-Tahun-2018> (sitasi 05 Oktober 2015).
- Khalili, G., Janghorbani, M., Saryazdi, H., & Emaminejad, A. (2013). Effect of preemptive and preventive acetaminophen on postoperative pain score: a randomized, double-blind trial of patients undergoing lower extremity surgery. *Journal of Clinical Anesthesia*, (25)3, pp. 188–192.
- Kumar, A., Kumari, R., Kumar, S., & Raj, P. (2018). Assessment of postoperative analgesia after intraperitoneal instillation of lornoxicam in laparoscopic appendectomy: a randomized study. *International Surgery Journal*, (5)8, pp. 2846.
- Lasander, C., Rumende, R., & Huragana, J. (2016). Pengaruh Teknik Distraksi terhadap Penurunan Intensitas Nyeri pada Pasien Post Operasi Appendiksitis di RS Pancaran Kasih Manado. *E-Jurnal Sariputra*, (3)2, pp. 1–6.
- Lukas, S., Viega, S., & Supusepa, D. A. (2017). Drug Related Problems (DRPs) Berdasarkan Kategori PCNE V6.2. *Social Clinical Pharmacy Indonesia Journal*, (1)2, pp. 77–83.

- McGuire, L. S., & Slavin, K. (2020). Revisiting the who analgesic ladder for surgical management of pain. *AMA Journal of Ethics*, (22)8, pp. 695–701.
- Nugroho. (2011). *Asuhan Keperawatan maternitas, anak, bedah dan penyakit dalam*. Yogyakarta: Nuha Medika, pp. 35-47.
- Petroianu, A. (2012). Diagnosis of acute appendicitis. *International Journal of Surgery*, (10)3, pp. 115–119.
- PIONAS. (2015). Analgesik Non-Opioid. Available from <http://pionas.pom.go.id/ioni/bab-4-sistem-saraf-pusat/47-analgesik/471-analgesik-non-opioid> (sitasi tanggal 12 Oktober 2020).
- Price, S. A W. L. M. (2012). *Patofisiologi: Konsep Klinis Proses-Proses Penyakit*. Jakarta: EGC, pp. 69-80 .
- Ramadani, L., Hidayat, N., & Fauzia, D. (2015). Gambaran Penggunaan Analgetik pada Pasien Rawatan Intensif di RSUD Arifin Achmad Provinsi Riau Periode Januari - Desember 2015. *Jom Fk*, (4)2, pp. 1–13.
- Salih, A. M., Kakamad, F. H., & Abbas, M. H. (2016). report Peer Reviewed | OPEN Acute cholecystitis with perforated appendicitis : The first reported case. *J Case Rep Images Surg*, (2)1, pp. 57–59.
- Sjamsuhidajat, R. (2016). *Buku Ajar Ilmu Bedah Sjamsuhidajat De Jong Sistem Organ Dan Tindakan Bedahnya (2 Edisi 4*. Jakarta: Penerbit Buku Kedokteran EGC.
- Suman, R., Mohanty, I. R., & Deshmukh, Y. A. (2014). The concepts of drug utilization study. *World Journal Of Pharmacy and Pharmaceutical Sciences*, (3)10, pp. 352–363.
- Tejovathin, R., Babu, N., & Debnath, S. (2017) . An Overview of Food & Drug Interactions. *Pharma Times*, (49)4, pp. 10–15.
- Windy & Sabir, M. (2016). Perbandingan Antara Suhu Tubuh, Kadar Leukosit, dan Platelet Distribution Width (PDW) Pada Apendisitis Akut dan Perforasi. *Jurnal Kesehatan Tadulako*, (2)2, pp. 24–32.
- Zulfikar, F., Budi, P., & Wiratmo. (2015). Studi Penggunaan Antibiotik pada Kasus Bedah Apendiks di Instalasi Rawat Inap RSD dr . Soebandi Jember Tahun 2013. *E-Jurnal Pustaka Kesehatan*, (3)1, pp. 44-4