Effects of Pipemidic Acid, Phenazopyridine HCL and Sodium Diclofenac on Pain Perception Following Endoscopic Urological Surgery: Double-blinded Randomized-Controlled Trial

Prahara Yuri[1], Zulfikar Ali[2], Nur Rasyid[1], Ponco Birowo[1]

[1] Department of Surgery, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
[2] Department of Surgery, Kardinah Hospital, Tegal, Central Java, Indonesia.

Corresponding Author:
Ponco Birowo, MD, PhD. Division of Urology, Department of Surgery, Faculty of Medicine Universitas Indonesia. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. email: ponco.birowo@gmail.com.

ABSTRAK

Tujuan: *untuk mengevaluasi efek analgesik, efek samping, dan keamanan dari obat setelah prosedur endoskopi di bidang urologi.* ***Metode:*** *80 pasien yang menjalani operasi endoskopi di Rumah Sakit Kardinah, Tegal sejak Juni sampai Juli 2015 dibagi jadi empat kelompok. Kelompok eksperimental diberikan analgesik selama 4 hari, (A) asam pipemidat 400 mg bid, atau (B) phenazopyridine 200 mb tid, atau (C) diklofenak 50 mg bid, dan (D) plasebo tid. Efek analgesik dinilai dengan Visual Analog Scale (VAS). Hubungan antar variabel dinilai dengan menggunakan Cramers V dan Kruskall Wallis.* ***Hasil:*** *prosedur endoskopi urologi terdiri dari 30 pasien menjalani URS, 6 pasien litotripsi, 17 pasien TURP, 24 pasien pengangkatan dj stent, dan 3 pasien sistoskopi. Rerata usia kelompok A, B, C, dan D adalah 50.1 (13.7), 50.7 (14.8), 49.1 (13.4), dan 49.6 (14.3) tahun, dan rerata lama followup adalah 7 hari. Nilai VAS dari seluruh kelompok eksperimental lebih rendah dari kelompok kontrol pada hari pertama sampai hari ke tujuh setelah prosedur endoskopi ($p<0.05$). Pada kelompok eksperimental, tidak terdapat perbedaan antara kelompok B dan C ($p>0.05$). Kelompok A memperlihatkan efek analgesik yang lebih baik daripada B dan C ($p<0.05$). Tidak didapatkan efek samping yang serius pada seluruh kasus.* ***Kesimpulan:*** *penggunaan analgesik oral efektif untuk meredakan nyeri setelah operasi endoskopi di bidang urologi. Asam pipemidat memiliki efek analgesik yang superior.*

Kata kunci: *asam pipemidat, phenazopyridine, diklofenak, endoskopik , visual analog scale.*

ABSTRACT

Aim: *to evaluate the analgesic effect, the side effects and the safety of analgesics following endoscopic urological procedure.* ***Methods:*** *eighty patients who underwent endoscopic urological surgery at Kardinah Hospital, Tegal from June to July 2015 were divided into four groups. The experimental group was administered analgesic for 4 days pipemidic acid (A) 400 mg bid, or phenazopyridine (B) 200 mg tid, or sodium diclofenac (C) 50 mg bid and the control (D) group was administered placebo tid for 4 days. The analgesic effects were assessed using Visual Analog Scale (VAS). Association between variables was assessed using Cramers V and Kruskall Wallis.* ***Results:*** *the endoscopic urological procedures consisted of 30 patients for URS, 6 patients for lithotripsy, 17 patients for TURP, 24 patients for removal JJ stent and 3 patients for cystoscopy. The mean age of group A, B, C and D (control) was 50.1 (13.7), 50.7 (14.8), 49.1 (13.4), and 49.6 (14.3) years, respectively, and follow-up period was 7 days. The VAS score in all experimental groups was less than control group on day 1 to 7 following endoscopic urological procedures ($p<0.05$). In the experimental group, there was no*

difference between groups B and C ($p>0.05$). Group A demonstrated a more favourable analgesic effect than B and C ($p<0.05$). No serious side effects were detected in any of the cases. ***Conclusion:*** *we conclude that oral analgesics are effective for pain relief following endoscopic urological surgery. Pipemidic acid was found to have a superior analgesic effect than phenazopyridine HCl and sodium diclofenac.*

Keywords: *pipemidic acid, phenazopyridine, sodium diclofenac, endoscopic urology, visual analog scale.*

INTRODUCTION

Pain is a common symptom following endoscopic urological surgery, and the need for effective pain management is a major concern. In general, regional or local anaesthesia demonstrates distinct advantages and disadvantages in terms of postoperative morbidity.[1,2] Therefore, general or regional anesthesia has been replaced by opioids, sedatives, non-steroidal anti-inflammatory drugs (NSIADs), and topical anesthetics for pain management.[3,4] The ideal postoperative analgesic treatment should provide rapid and effective pain relief, offer a low incidence of adverse effects and result in a minimal impact on organ systems with no significant interaction with other pharmacological agents.[1] The mechanism of acute pain following endoscopic urological surgery remains unclear. Acute postoperative pain is mainly associated with the operation itself and the duration of operation time.[5]

Until now, many urologists have not yet studied the outcome of acute post-operative pain which the patients perceive as a serious problem and which accompanies most postoperative complications.[5] In addition to NSAIDs, there are several drugs known as anti-microbial and uroseptic that have an analgesic effect, such as phenazopyridine hcl and pipemidic acid.[6–8] Based on the degree of pain, urological procedures, such as extracorporeal shock wave lithotripsy (ESWL), endoscopic urological surgery (transurethral, endoscopic percutaneous) and trans-vaginal surgery are still included in the category of mild pain following surgery.[9]

Phenazopyridine relieves pain associated with bladder spasms and postoperative ureteral stent or in-dwelling urinary catheter discomfort.[4,6] Pipemidic acid is an anti-microbial group that is used as a urinary antiseptic and reduces pain caused by an acute tract infection.[7,10,11] The analgesic effect of pipemidic acid following endoscopic urological surgery is controversial and, to date, there are no relevant study reports to support the claim. The analgesic effect might be caused by optimization of a pipemidic acid autotaxin inhibitor.[12–15] Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for their potent antipyretic and analgesic effects. These drugs reduce pain following surgery by preventing synthesis and release of prostaglandins at the site of surgical trauma by inhibition of cyclo-oxygenase-2 (COX-2).[1]

The clinical indication and analgetic effect of pipemidic acid, phenazopyridine and sodium dicofenac remain unclear. The purpose of this prospective, randomized study was to compare the effectiveness of analgesia and side-effects of pipemidic acid, phenazopyridine hcl and sodium diclofenac for postoperative analgesia following endoscopic urological surgery.

METHODS

Study Design

This study was a prospective, randomized, double-blind, placebo-controlled trial. The study compared the analgesic effects following endoscopic urological surgery. Pain perception was assessed from the first day until the seventh day following surgery. Analgesic drugs were administered for 4 days following surgery. The analgesic effects were assessed using the Visual Analog Scale (VAS). The eligibility criteria of subject was age ≥17 years old who underwent endoscopic urological surgery, such as transurethral resection transurethral of prostate (TURP), ureterorenoscopy (URS), lithotripsy of bladder stone, removal double-J stent and cystoscopy. No history was presented of psychotic mental illness, organic psychiatric conditions and other mental illnesses, of severe pain-induced illnesses and malignancy. The

patient underwent open surgery conversion after exclusion of endoscopic urological surgery. The study was initiated after obtaining the approval of the Institutional Ethics Committee Kardinah Hospital. Ref: 071/008/2015.

Intervention

The patients who underwent endoscopic urological surgery (transurethral resection of prostate (TURP), lithotripsy of bladder stone, ureterorenoscopy (URS), removal JJ stent and cystoscopy) at Kardinah Hospital, Tegal from June 2015 to July 2015 were divided into four groups. The experimental groups (A, B and C) consisted of 20 patients in each group while the control group (D) consisted of 20 patients. The experimental group was administered antibiotics, anticoagulant and analgetic medication. In group A, patients were administered pipemidic acid 400 mg bid for 4 days. In group B, patients were administered phenazopyridine 200 mg tid for 4 days. In group C, 50 mg of sodium diclofenac was applied twice a day for 4 days. Control group D was administered antibiotics, anticoagulant and placebo medication tid for 4 days. All groups were randomized by block random system. All patients were remained consistant for the duration of this study. The analgesic effects were assessed using the Visual Analog Scale (VAS).

Statistical Analysis

Age, gender, day of catheterization, operation time, hospitalization, patient satisfaction, adverse events, patient complaints and VAS scale for each patient were recorded. Statistical analysis was recorded using one way ANOVA, Kruskal Wallis; Cramers V, Mann U Whitney, and results were compared between the four groups. A P value of less than 0.05 was considered to be statistically significant.

RESULTS

Patients characteristics are summarized in **Table 1**. The average age of the 80 patients (50 males and 30 females) was 49.9 (13.8) years old. The endoscopic urological procedures included 30 patients for URS, 6 patients for lithotripsy of bladder stone, 17 patients for TURP, 24 patients for removal JJ stent and 3 patients for cystoscopy. (**Figure 1**) The overall postoperative VAS scale following endoscopic urological surgery was summarized in **Table 2 and 3**.

Table 1. Subject's characteristics

Variables	Overall	Pipemidic Acid	Phenazopyridine HCl	Sodium Diclofenac	Placebo
Age, mean (SD)	49.9 (13.8)	50.1 (13.7)	50.7 (14.8)	49.1 (13.4)	49.6 (14.3)
Day(s) of catheterization, mean (SD)	1.4 (1.5)	1.3 (1.5)	1.4 (1.5)	1.5 (1.5)	1.4 (1.5)
Operation time, mean (SD)	33.5 (21.6)	33.3 (25)	35.1 (21.2)	34 (21)	31.5 (20.1)
Hospitalization, mean (SD)	1.5 (1.5)	1.4 (1.5)	1.5 (1.7)	1.6 (1.5)	1.5 (1.5)
Diagnosis, n (%)					
- Ureteral stone	29 (36.3)	7 (35)	7 (35)	8 (40)	7 (35)
- Ureteral stenosis	1 (1.3)	0 (0)	1 (5)	0 (0)	0 (0)
- Bladder stone	6 (7.5)	2 (10)	1 (5)	1 (5)	1 (5)
- Benign prostate hyperplasia (BPH)	17 (21.3)	4 (20)	4 (20)	5 (25)	4 (20)
- JJ Stent in situ	24 (30)	7 (35)	6 (30)	5 (25)	6 (30)
- Voiding dysfunction	3 (3.8)	0 (0)	1 (5)	1 (5)	1 (5)
Gender, n (%)					
- Male	50 (62.5)	12 (60)	11 (55)	14 (70)	13 (65)
- Female	30 (37.5)	8 (40)	9 (45)	6 (30)	7 (35)

Table 1. Subject's characteristics

Variables	Overall	Pipemidic Acid	Phenazopyridine HCl	Sodium Diclofenac	Placebo
Management, n (%)					
- URS/Lithotripsy	36 (45)	9 (45)	9 (45)	9 (45)	9 (45)
- TURP	17 (21.3)	4 (20)	4 (20)	5 (25)	4 (20)
- DJ stent removal/ Cystoscopy	27 (33.7)	7 (35)	7 (35)	6 (30)	7 (35)
Catheterization, n (%)					
- Yes	56 (70)	13 (65)	14 (70)	15 (75)	14 (70)
- No	24 (30)	7 (35)	6 (30)	5 (25)	6 (30)
JJ Stent insertion, n (%)					
- Yes	14 (17.5)	3 (15)	3 (15)	4 (20)	4 (20)
- No	66 (82.5)	17 (85)	17 (85)	16 (20)	16 (20)
Patient satisfaction, n (%)					
- Yes	69 (86.3)	20 (100)	19 (95)	18 (90)	13 (65)
- No	11 (13.7)	0 (0)	1 (5)	2 (10)	7 (35)
Urinalysis, mean (SD)					
- Ph	5.9 (0.8)	5.8 (0.7)	5.8 (0.7)	6.3 (0.9)	6 (0.6)
- Specific gravity	1.01 (0.007)	1.013 (0.006)	1.015 (0.008)	1.016 (0.008)	1.015 (0.007)
Erithrocituria, n (%)					
- Yes	58 (72.5)	14 (70)	13 (65)	16 (80)	15 (75)
- No	22 (27.5)	6 (30)	7 (35)	4 (20)	5 (25)
Leucocyturia, n (%)					
- Yes	63 (78.8)	17 (85)	17 (85)	14 (70)	15 (75)
- No	17 (21.2)	3 (15)	3 (15)	6 (30)	5 (25)

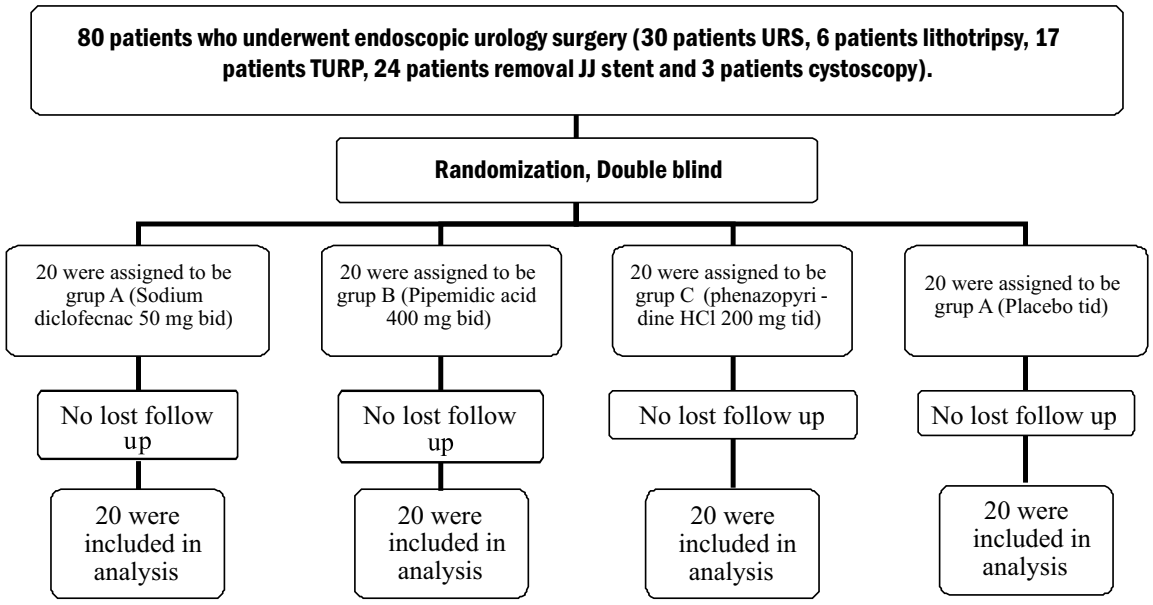

Figure 1. Consort flow diagram of the current randomized controlled trial

Table 2. Postoperative VAS Score for all endoscopic urological surgeries

Post-operative	Overall, mean (SD)	Pipemidic acid, mean (SD)	Phenazopyridine HCl, mean (SD)	Sodium Diclofenac, mean (SD)	Placebo, mean (SD)	p value
Day 1	5.3 (2.6)	3.2 (1.8)	5.9 (2.2)	5.4 (2.8)	6.7 (2.2)	<0.001
Day 2	4.1 (2.2)	2.5 (1.8)	4.4 (1.4)	4.0 (2.5)	5.6 91.9)	<0.001
Day 3	3.0 (1.9)	1.6 (1.6)	3.2 (1.2)	3.0 (2.2)	4.4 (1.7)	<0.001
Day 4	2.4 (1.9)	1.3 (1.5)	2.4 (1.6)	2.5 (1.9)	3.6 (1.7)	0.001
Day 5	1.9 (2.0)	0.9 (1.4)	2.1 (1.8)	2.4 (2.5)	2.7 (1.9)	0.013
Day 6	1.6 (1.9)	0.5 (0.8)	1.8 (1.8)	2.0 (2.5)	2.1 (1.9)	0.014
Day 7	1.3 (1.8)	0.3 (2.5)	1.5 (1.5)	1.6 (2.5)	1.8 (1.8)	0.006

Table 3. Postoperative VAS score based on endoscopic urological surgery

Postoperative	TURP	URS/Lithotripsy	DJ Stent Removal/Cystoscopy	P
Day 1	6.9 (2.5)	5.1 (2.4)	4.5 (2.6)	0.014
Day 2	4.7 (2.2)	4.4 (2.3)	3.4 (2.0)	0.134
Day 3	3.5 (1.8)	3.3 (1.9)	2.4 (1.9)	0.162
Day 4	2.4 (1.4)	2.8 (1.9)	1.9 (1.9)	0.241
Day 5	2.0 (1.7)	2.3 (2.2)	1.6 (1.9)	0.318
Day 6	1.8 (1.6)	1.8 (2.1)	1.2 (2.0)	0.242
Day 7	1.1 (1.4)	1.5 (1.8)	1.2 (2.0)	0.566

The comparison of median age of groups 1, 2, 3 and 4 were 50.1, 50.7, 49.1 and 49.6 years, respectively, compared with 44.98 years in group 2 (p=0.05). Leukocyturia was found in 17 patients in group 1, 17 patients in group 2, 14 patients in group 3 and 15 patients in group 4 (p=0.57). The most common diagnosis was ureteral stones in 29 patients. Catheterization and double-J stent insertion were undertaken in 56 and 14 patients, respectively.

Decrease of VAS scale following endoscopic urological surgery was statistically significant from day one until day seven (p<0.05). However, if we compare the various methods of endoscopic urological surgery, the decrease of VAS scale was only statistically significant on day one (p=0.014), but not statistically significant during the other days (p>0.05). In the experimental group, there was no difference between group B and C (p>0.05). Group A demonstrated a better analgesic effect than B and C (p<0.05). (**Table 5** and **Figure 2)** No serious side effects were detected in any of the cases (**Table 4**). Eleven patients complained of severe acute postoperative pain with VAS 7-10 (one patient in group 1, 3 patients in group 2, 3 patients in group 3 and 4 patients in group 4). This was optimally controlled with ketoprofen 50 mg suppositories of non-steroidal anti-inflammatory drugs (NSAIDs).

DISCUSSION

Major advancements have been made in recent times in urological treatments which constituted the majority of urological conditions. In the past, treatment involved mainly invasive procedures. In recent years, non-invasive procedures, such as endourological surgery, have been made available.[5] Pain management is a common and complex issue for the urologist. Unrelieved pain is a major medical problem. In the end of the 1990s, the physiological and psychological consequences of acute and chronic pain became well-recognized[16], and pain management during transurethral procedures is now well established.[1,2] However, many urologists have not yet studied the relief of acute postoperative pain following endoscopic

Table 4. Most frequent adverse events and patient complaints

	Overall	Pipemidic Acid	Phenazopyridine HCl	Sodium diclofenac	Placebo
Additional analgetic, n (%)	11 (13.8)	1 (5)	3 (15)	3 (15)	4 (20)
Fever, n (%)	5 (6.3)	1 (5)	1 (5)	1 (5)	2 (10)
Nausea, n (%)	24 (30)	4 (20)	6 (30)	6 (30)	8 (40)
Vomitus, n (%)	6 (7.5)	0 (0)	1 (5)	2 (10)	3 (15)
Abdominal discomfort, n (%)	14 (17.5)	0 (0)	4 (20)	3 (15)	7 (35)
Skin rash, n (%)	1 (1.3)	0 (0)	0 (0)	0 (0)	1 (5)

Table 5. Post hoc analysis

		P value for VAS Score						
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Pipemidic acid	Phenazopyridine HCl	<0.001	0.001	0.003	0.031	0.017	0.011	0.002
	Sodium Diclofenac	0.01	0.046	0.036	0.039	0.018	0.023	0.042
	Placebo	<0.001	<0.001	<0.001	<0.001	0.002	0.001	0.001
Phenazopyridine HCl	Sodium Diclofenac	0.415	0.592	0.782	1	0.923	0.966	0.53
	Placebo	0.198	0.044	0.012	0.022	0.275	0.526	0.571
Sodium diclofenac	Placebo	0.103	0.044	0.035	0.049	0.481	0.529	0.299

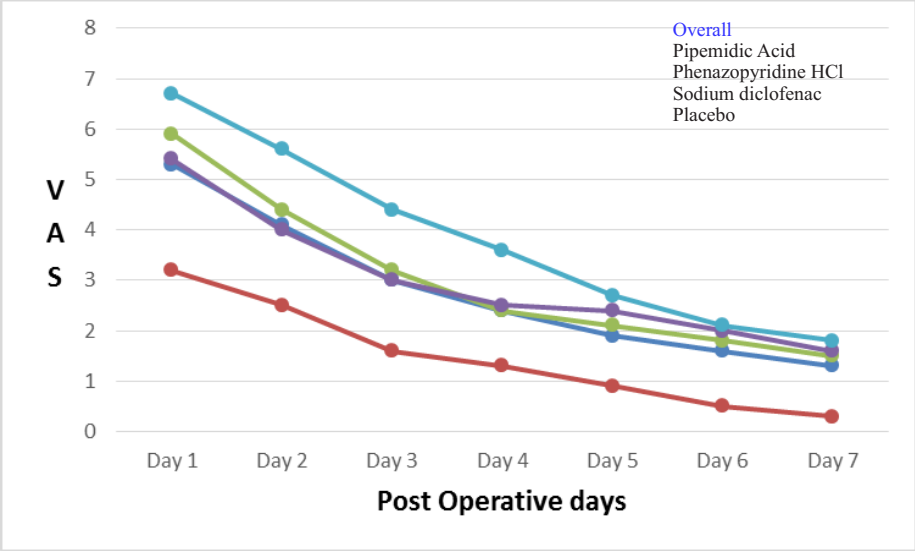

Figure 1. Pain scale changes on the Visual Analog Scale (VAS) – (p<0.05)

urological surgery. The goal of pain management after endoscopic treatments is to relieve pain and, keep the side effects to a minimum at the same time.[17]

Pain induced by endoscopic treatments is not the result of tissue injury alone and indeed has no significant effect. Cystoscopy usually causes pain due to preoperative anxiety and postoperative patients often suffer a urinary tract irritation following surgery.[4] However, in TUR-P, the resected adenoma cannot be rationally associated with pain induction, since the major causes of TUR-P pain are bladder spasms, catheter-related pain and capsule offense.[1,6] An in-dwelling

urinary catheter is a foreign body positioned in the bladder and can often cause severe pain and discomfort and impair the quality of life of the patient. The presence of a urinary catheter can trigger the bladder muscle to go into spasm in an effort to expel the catheter. This spasm leads to cramping lower abdominal pain.

The placement of ureteral stent following ureteroscopy remains a common practice. Stents have been routinely placed to facilitate passage of residual stone fragments, prevent ureteral stricture formation and renal colic secondary to ureteral edema. Unfortunately, ureteral stenting continues to result in significant patient morbidity, including flank pain, lower abdominal or loin discomfort, urinary urgency, urinary frequency, hematuria, infection, encrustation and migration. It has been reported that 38% to 80% of patients experience stent-related symptoms. To address this problem, modifications in ureteral stent design have been used, including self-retaining designs, softer biomaterials, dual durometer stents, reduced caliber configurations, biostable materials and biodegradable stents.[18] Postoperative ureteral stent discomfort may be resolved by these modifications.[6]

Current approaches for the management of catheterization/ureteral, stent-related pain/ discomfort include the use of non-steroidal anti-inflammatory medications, oral narcotics, oral anticholinergic medications (oxybutynin or tolterodine), drug-eluting/coated stents, and/ or oral local anesthetics (phenazopyridine). The efficacy of these medications in the treatment of pain/discomfort needs to be clarified and they are prescribed based mainly on intuition and assumption of good clinical practice.[18] The analgesic effect of pipemidic acid still requires further clarification and remains a controversial matter. No study to date has compared the analgesic effect of pipemidic acid, phenazopyridin and NSAID following endoscopic urological treatments.

The clinical indication of phenazopyridine remains unclear. It has been used clinically in conditions with increased bladder sensation, such as cystitis and bladder pain syndrome/interstitial cystitis. Phenazopyridine (2,6-diamino-3-[phenyl-azo]pyridine) hydrochloride has been used clinically as a local anesthetic/analgesic to provide symptomatic relief of pain in certain conditions, such as cystitis and urethritis. In addition, this drug is being used as a therapeutic option in patients with chronic bladder pain syndrome/interstitial cystitis (BPS/IC), and also hydrodistention, amitriptyline or pentosan polysulfate sodium. But there is little information available to date on the mode of action of the drug, i.e. influence to the sensory mechanisms, which have been referred to in the afferent functions in the rat.[19] Phenazopyridine HCl is effective for early acute pain relief following cystoscopy[4], management of postoperative ureteral stent discomfort,[6,18] and catheterization discomfort.[6]

NSAIDs for analgesia after surgery is a controversial matter, due to increased risk of post-operative bleeding by inhibition of the other isoforms of cyclo-oxygenase, causing anti-platelet activity.[1] Diclofenac sodium is an NSAID. NSAIDs are effective analgesics without the undesirable side effects associated with opioids, such as sedation, respiratory depression, nausea and vomiting. They inhibit the synthesis and the release of prostaglandins at the site of surgical trauma by inhibition of cyclo-oxygenase-2 (COX-2), which responsible for pain, fever and vasodilatation in response to trauma.[17] NSAIDs are known to decrease the incidence of bladder spasms through the reduction of the amount of prostaglandins released. Moreover, NSAIDs may help reduce postoperative edema, resulting in successful early catheter removal.[1] In a further study, non-steroidal anti-inflammatory drugs have demonstrated strong antimicrobial properties when tested against a large number of gram-positive and gram-negative bacteria. The MIC range was from 50-200 Ìg/mL in most of the cases and recorded even lower in some instances. Diclofenac is suggested to possess the capacity to treat urinary tract infections caused by drug-resistant *E. coli* strains.[20]

Pipemidic acid (HPPA), 8-ethyl-5, 8-dihydro-5-oxo-2-(1-piperazinyl)-pyrido[2,3-d] pyrimidine-6- carboxylic acid, is a therapeutic agent for urinary tract infections due to its antibacterial activity against gram-negative, and some gram-positive bacteria.[7,8,10,11,13,21] The

analgesic effect of pipemidic acid remains unclear and association with optimalization of pipemidic acid autotaxin inhibitor has been reported.[12] The ectoenzyme autotaxin (ATX) possesses lysophospholipase D phosphodiesterase and, to a lesser extent, nucleotide pyrophosphatase activities. In 1992, the ATX protein was purified and characterized from melanoma cell-conditioned medium, after which it was assigned to the nucleotide pyrophosphatase phosphodiesterase subfamily of alkaline phosphatases based on sequence homology.[22] Subsequently, ATX was shown to be the lysophospholipase D enzyme responsible for synthesis of the bioactive lipid lysophosphatidic acid (LPA) in vivo.[12]

Recent work has shown that ATX plays a critical role in normal human development and disease. ATX has been linked to cancer progression, multiple sclerosis, obesity, diabetes, Alzheimer's disease and chronic pain through the production of LPA.[12,22] One study reports a convenient diversification strategy to generate structure-activity relationship (SAR) data in the hope of better understanding ATX inhibitor recognition, and in identifying more potent analogs. In this study, the derivatization of pipemidic acid with commercially available isothiocyanate building blocks was identified as a facile route to a range of analogs of compound 1 bearing various substituents on the phenylthiourea motif.[12]

Lysophosphatidylcholine (LPC, lysolecithin) is an important cell signaling molecule among lysophospholipids. It is a major plasma lipid component that transports fatty acids and choline to tissues, and is produced under physiological and pathological conditions.[14] Recent reports suggest that LPC modulates pain signaling. LPC treatment of the aphenous or sciatic nerve–induced neuropathic pain, such as mechanical allodynia and thermal hyperalgesia, as well as demyelination and up-regulation of pain-related proteins in the dorsal root ganglion (DRG). However, the molecular mechanisms underlying LPC-induced neuropathic pain-like symptoms remain to be determined.[15] More recently, a study reported that intrathecal (i.t.) injection of lysophosphatidic acid (LPA) induces mechanical allodynia and thermal hyperalgesia, as well as demyelination of dorsal root and upregulation of pain-related proteins in the DRG and spinal cord via the LPA1 receptor.[14] Autotaxin (ATX), is responsible for the conversion of LPC to LPA, and is abundantly expressed in central and peripheral nerve tissues, especially in cerebrospinal fluids.[14,15,23]

This study had several limitations. First, this study had fewer sample in randomization and the study population was limited in rural hospital in Central Java. Further research is necessary to develop medications, improve design or modifications in surgical techniques that may effectively treat and/or prevent pain-related endoscopic treatment. This investigation provides a sound foundation for future studies to assess the ability of oral agents to reduce pain following endoscopic urological surgery.

CONCLUSION

The study suggests that pipemidic acid, phenazopyridine HCl and sodium diclofenac, as oral analgesics, have been proven effective for pain relief following endoscopic urological surgery without inducing any side effects. Pipemidic acid has been found to have more superior analgesic effect than phenazopyridine HCl and sodium diclofenac.

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