ORIGINAL RESEARCH

Diclofenac versus Combination of Dexketoprofen and Hyoscine N-Butyl Bromide in the Treatment of Renal Colic in the Emergency Room Setting: A Single-Blinded Randomized Controlled Trial in a Tertiary Government Hospital in the Philippines

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Introduction: Renal colic pain is a very severe pain usually being consulted at the emergency room. New pain relievers together with combination of other drugs is used for symptomatic relief. This study compared the efficacy and tolerability of Diclofenac versus Dexketoprofen with Hyoscine N-butyl bromide (HNBB) in the management of acute renal colic at the emergency room.
Methodology: This was a single blind, randomized prospective study done from June 1, 2017 to August 31, 2017 at the emergency department of the Jose Reyes Memorial Medical Center. Allocation and randomization were done into two treatment groups: the Diclofenac and Dexketoprofen + HNBB. Subjectivity of pain relief was based using visual analogue score (VAS), this was taken before the treatment and 15, 30 and 60 minutes after administration of treatment.
Results: Twenty nine (29) patients were grouped into two: Dicloenac group (n=15) and Dexketoprophen + HNBB group (n= 14). Pain reduction in the combination group had a faster pain relief compared to Diclofenac alone with a 41% and 17% decline, respectively. The study showed that a faster pain relief was achieved with the Dexkoprophen + HNBB combination compared to Diclofenac alone.
Conclusion: Timing and onset of pain control in patients presenting with renal colic pain is essential in the emergency room setting to provide adequate relief. The use of the combination therapy of Dexkotoprofen + HNNB may have a significant advantage in terms of rapid onset of relief.

Keywords: diclofenac, dexketoprofen, hyoscine N-butyl bromide, renal colic, visual analogue score

Introduction

Renal colic from symptomatic urolithiasis is a relatively common complaint in the emergency room.[1] The classic presentation of a ureteric colic includes an acute onset colicky flank pain radiating to the groin, often associated with nausea, vomiting, and sweating.[2] Since most ureteric stones will pass spontaneously, close observation with analgesia for the pain is the preferred approach for newly symptomatic patients.[3]

Intensity of pain is usually measured by the use of the Visual Analogue Score (VAS) where pain is ranked by intensity from 1, no pain, to 10, representing worst pain experienced. VAS of 1-3

refers to mild pain, 4-7 to moderate pain and >7 to severe pain.[4] In moderate to severe pain that usually characterizes pain from ureteric colic, non-steroidal anti-inflammatory drugs (NSAIDs) and opiates are preferred regimens.[5]

NSAIDs for pain relief are recommended due to their capability to decrease ureteral smooth muscle tone. The severe pain associated with acute renal colic is caused by increased tension of the walls of the urinary tract due to urinary flow obstruction. Intensifying tension in the renal pelvis then stimulates the release of prostaglandins that leads to ureteric spasm and eventual pain.[6] NSAIDs have been commonly utilized as treatment of acute renal pain as they directly inhibit the synthesis of prostaglandins and have been proven to achieve greater reduction of pain scores as compared to opioids. They also have been shown to further decrease need for additional analgesia after the short-term period.[7]

One of the most commonly used NSAIDs is Diclofenac. In a study by Shaden, et al., Diclofenac administered intramuscularly proved to be superior to opioids for pain relief in patients suffering from renal colic.[8] However, this drug is contraindicated for those with renal failure and other kidney derangements, making it not suitable for every patient.[9]

Studies regarding Dexketoprofen trometamol have shown good safety and efficacy in the management of pain from acute renal colic.[10] In the treatment of mild to moderate pain, such as musculoskeletal pain, dental pain and dysmenorrhea, evidences show that dexketoprofen exhibits a good safety profile, and has faster analgesic onset when compared to Ibuprofen.[11,12] Combination of Dexketoprofen with Hyoscine N-butyl bromide is likely to be synergistic, at which the latter is a known anti-spasmodic agent effective in the treatment of smooth muscle spasms.[13]

This study was done to evaluate and compare the efficacy and tolerability of Diclofenac versus Dexketoprofen with Hyoscine N-butyl bromide in the management of acute renal colic when administered as an intramuscular injection in the emergency room setting.

This study aims to determine if the combination of Dexketoprofen and Hyoscine N-butyl bromide would exhibit superior efficacy to Diclofenac in the pain management of patients with renal colic in the emergency room setting.

Review of Related Literature

Ureteric colic is described as acute, colicky pain often radiating to the groin caused by an obstruction at the narrowest portions of the urinary tract by calculi, most commonly occurring at the ureteropelvic junction (UPJ), near the pelvic brim, and at the ureterovesical junction (UVJ).[14] As the stone passes down the ureter, it may cause ureteric colic causing sudden severe pain in the loin, radiating to the groin, perineum, testis or to the labia, associated with vomiting and sweating. If infection occurs, fever and chills may be seen. The urine may be smoky and, at times, blood-stained. If the stony impacts, the severe pain of the ureteric colic gradually subsides.[15]

NSIADs have been shown to achieve greater efficacy in pain control, have longer duration of action with less need for adjunct analgesia, and are considered as a common treatment for renal colic pain. The effectiveness of NSAIDs may be attributed to prostaglandin production as part of the pathophysiology of ureteric colic.[16] There is also no risk for drug-seeking behavior in patients taking NSAIDs for pain control as compared to those under an opioid regimen.

The patient's general well being, presence of co-morbidities, age, and individual preferences should be taken into account in formulating an appropriate pain management plan. Opioid analgesics may be prescribed in addition, or as an alternative, to NSAIDs for patients with chronic renal impairment or those with history of peptic ulcer disease.[17]

Diclofenac is most commonly the first choice for renal colic because it is the NSAID with the most compelling evidence of effectiveness in the management of pain in these patients. The injectable preparation is indicated for the immediate treatment of renal colic pain and may be administered intramuscularly. Oral or rectal forms may be prescribed for continuous pain management.[18] Diclofenac is a phenylacetic acid with potent anti-inflammatory, analgesic and antipyretic uses, reversibly inhibiting

cyclooxygenase leading to reduced synthesis of prostaglandin precursors. It is rapidly absorbed with bioavailability of 100% intravenously and 75-100% intramuscularly and with a half-life of approximately 1-2 hours.[19]

Diclofenac is contraindicated for those with history of myocardial infarction in the past 12 months as it may cause an increased risk of serious cardiovascular thrombotic events, including cerebrovascular stroke, associated with prolonged use. It may also cause an increase susceptibility to gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, and with the elderly patients being the most vulnerable population.[19]

Dexketoprofen trometamol is a water-soluble dextrorotatory enantiomer of the NSAID ketoprofen and is used as an analgesic and inflammatory agent by inhibiting prostaglandin synthesis.[20] This effect is due to the S(+)-enantiomer which is responsible to approximatly 2-fold greater potency of the drug based on animal studies.[21] A parenteral solution of dexketoprofen trometamol can be used in clinical situations wherein the drug cannot be administered orally or where parenteral route offers more sense such as in cases where faster onset of analgesia and avoidance of drug absorption hindrances due to vomiting, as can occur in renal colic, are required.[22] Studies have shown that Dexketoprofen exhibits good tolerability via intramuscular injection as well as intravenous infusion or bolus for the management of moderate to severe pain.[23] Onset of analgesic effect is rapid, with peak analgesic effect within the first 45 minutes. Duration after administration is usually 8 hours. There is no evidence of unfavorable drug-to-drug interaction between Dexketoprofen and anti-spasmodic agents, such as Hyoscine N-butyl bromide.[25]

Hyoscine N-butyl bromide is an anti-muscarinic agent which blocks the action of acetylcholine at the parasympathetic nerve endings in muscles and glands and is possibly effective in the treatment of smooth muscle spasms, relieving moderate renal colic pain.[24] In comparing the effect of diclofenac alone and combination of diclofenac and hyoscine in short-term treatment of ureteric colic, pain relief assessment showed better pain control with combination of both drugs than with diclofenac alone. Possible side effects associated with HNBB include dry mucous membranes, photophobia, facial flushing, dry skin and constipation.[26]

Administration of analgesics by parenteral route, either intravenously or intramuscularly, is the preferred route for the management of acute severe pain from ureteric colic. Compared to oral route that has a slower onset and presents a disadvantage for patients with nausea, vomiting, intramuscular route of administration may prove to be the best method of administration due to its immediate effect and accessibility without the need for an intravenous line to be present.[27]

Patients and Methods

The present study used randomized trial with 28 subjects with a moderate to severe colic who presented at the emergency room of JRMMC from June 1, 2017 to August 31, 2017. The study included patients between 18-65 years old with confirmed diagnosis of ureteric colic, confirmed by imaging either via CT, ultrasound or x-ray. Patients who were pregnant, breastfeeding, with peptic ulcer disease, end stage renal disease, history of myocardial infarction, bleeding disorders and allergy to diclofenac, dexketoprofen or hyoscine-N-butyl bromide, and those who took pain medication 6 hours prior to assessment, were excluded from the study. The nature of the study was explained and informed consent was solicited.

Patients were randomly assigned to two treatment groups: one for pain management with Diclofenac, and one with Dexketoprofen + Hyoscine N-butyl bromide. Those who presented at the emergency room during odd numbered dates were given Diclofenac while patients who consulted during even numbered days were administered with Dexketoprofen + Hyoscine N-butyl bromide. The study is a single blinded study wherein the patients were unaware of which drug for pain was given to them. Medication was administered via intramuscular route to ensure immediate effect without requiring the insertion of an intravenous line.

Intensity of pain was assessed using a visual analogue score (VAS) by the resident who attended to the patient. Pain was rated from the score of 1 to 10 and recorded. VAS was taken before administration of treatment and 15, 30 and 60 minutes after treatment. This study was approved by the Institutional Review Board (IRB).

Study Subjects

Inclusion Criteria

Patients between the ages of 18 to 65 years old, with confirmed diagnosis of ureteric colic, confirmed by imaging either via CT scan, ultrasound or x-ray. Subjects must be able to provide a written informed consent for the study.

Exclusion Criteria

Patients who are pregnant, breastfeeding, with peptic ulcer disease, end stage renal disease, history of myocardial infarction, bleeding disorders and allergic to Diclofenac, Dexketoprofen or Hyoscine N-butyl bromide, and those who took pain medication 6 hours prior to assessment due to possible decrease in pain perception due to residual effects of the drug taken.

Statistical Analysis Plan

Descriptive analyses of data categorized as nominal were presented using frequency and percentages while continuous data were summarized using mean, median and standard deviation. Before and after treatment results were assessed using Wilcoxon Signed Ranks Test since data followed a free distribution while comparison of mean VAS difference between diclofenac and Dexketoprophen + HNBB groups was tested using Mann-Whitney T-Test.

The responsiveness of the patients to each treatment provided to them was calculated using effect size and standardized response mean. Effect size is defined as change in mean scores between baseline and observed given time after initial intake divided by the standard deviation of the pre-treatment Visual Analogue Score (VAS) while Standardized Response Mean is also mean VAS difference where divisor is standard deviation of the new/change score. Effect size and Standardized response mean ≥ 0.8 is considered significantly large.

Results

Table 2 shows the characteristic profile of the patients recruited for this study. Twenty nine (29) patients were included in this study of which 15 took Diclofenac medication alone while 14 took the combination treatment of Dexketoprophen + HNBB. Patients in the first group were characterized to mostly comprise females (3 out of 5), underwent Ultrasound and had Nephrolithiasis (right) impression. On the other hand, patients in the second group or those taking the combination of Dexketoprophen + HNBB were characterized as majority males (57%), also underwent ultrasound, and had nephrolithiasis (left). Patients in this group were also younger than the previous (48.57 vs 52) but had lower mean creatinine values (82.36 vs. 92.73). (Table 3.)

Table 4 and Figure 1 present the progress of relief in terms of Visual Analogue Score (VAS) for the two treatment groups, 1) Diclofenac and 2) Dexketoprophen + HNBB. Both groups showed improvement even as early as after 1 minute of intake. However, patients in the second group significantly showed better improvement up until after 15 minutes since medication intake due to its early response rate in terms of VAS.

Table 5 shows that statistically significant difference was observed in the mean values of VAS between a specific time interval and before modification (all p-values < 0.05).

In terms of percentage decline in the VAS scores of patients for each group, Table 6 really suggested that the combination of Dexketoprophen + HNBB has improved drastically to 41% after 1 minute. After 30 minutes and 60 minutes, the VAS scores difference from baseline in between groups were no longer statistically significant.

Table 4 revealed declining pain metrics, VAS, for 2 treatment groups, with patients in Dexketoprophen + HNBB. Pain reduction in the

Table 1. Normality assessment.

Time Interval	Type of Medicine	Shapiro-Wilk	
		Statistic	p-Value
Pain before Meds	Diclofenac	.861	.025
	Dexketoprophen + HNBB	.850	.022
1 min	Diclofenac	.829	.009
	Dexketoprophen + HNBB	.804	.006
7 mins	Diclofenac	.905	.115
	Dexketoprophen + HNBB	.821	.009
15 mins	Diclofenac	.898	.088
	Dexketoprophen + HNBB	.584	.000
30mins	Diclofenac	.421	.000
	Dexketoprophen + HNBB	.297	.000

a. Lilliefors Significance Correction
b. 60mins is constant when Type of Medicine = Diclofenac. It has been omitted.
c. 60mins is constant when Type of Medicine = Dexketoprophen + HNBB. It has been omitted.

Table 2. Demographic profile of patients (Categorical/Discrete Variables)

Demographic Profile	Type of Medicine		p-Value
	Diclofenac (15 patients)	Dexketoprophen + HNBB (14 patients)	
Sex			
Male	6 (40%)	8 (57%)	0.466
Female	9 (60%)	6 (43%)	
Total	15 (100%)	14 (100%)	
Radiologic Exam			0.139
Ultrasound	6 (40%)	10 (71%)	
CT-Scan	9 (60%)	4 (29%)	
Total	15 (100%)	14 (100%)	
Impression			0.469
Nephrolithiasis Bilateral	3 (20%)	1 (7%)	
Nephrolithiasis Left	1 (7%)	4 (29%)	
Nephrolithiasis Right	4 (27%)	2 (14%)	
Pelvolithiasis Right	0	1 (7%)	
Staghorn Calculus Left	1 (7%)	1 (7%)	
Staghorn Calculus Right	0	1 (7%)	
Ureterolithiasis Left	3 (20%)	1 (7%)	
Ureterolithiasis Right	2 (13%)	3 (31%)	
Ureterolithiasis Right;Cystolithiasis	1 (7%)	0	
Total	15 (100%)	14 (100%)	

Table 3. Demographic profile of patients (Categorical/Discrete Variables)

Demographic Profile	Type of Medicine		p-Value
	Diclofenac (15 patients)	Dexketoprophen + HNBB (14 patients)	
Age	52 ± 10.078	48.57 ± 13.137	0.585
Creatinine	92.73 ± 12.864	82.36 ± 13.585	0.042 < 0.05

Table 4. Changes in visual analogue scores (VAS) per time interval (Baseline and After 1, 15, 30 and 60 minutes)

Treatment Received	Pain before Meds		After 1 min		After 7 mins		After 15 mins		After 30 mins		After 60 mins	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Diclofenac (n=15)	8.867	0.990	7.400	1.549	4.333	1.543	1.733	1.163	0.200	0.561	0.000	.000a
Dexketoprophen + HNBB (n=14)	8.214	0.802	4.857	1.351	1.857	1.562	0.571	1.158	0.143	0.535	0.000	.000a

a. t statistic cannot be computed because the standard deviations of both groups are 0.

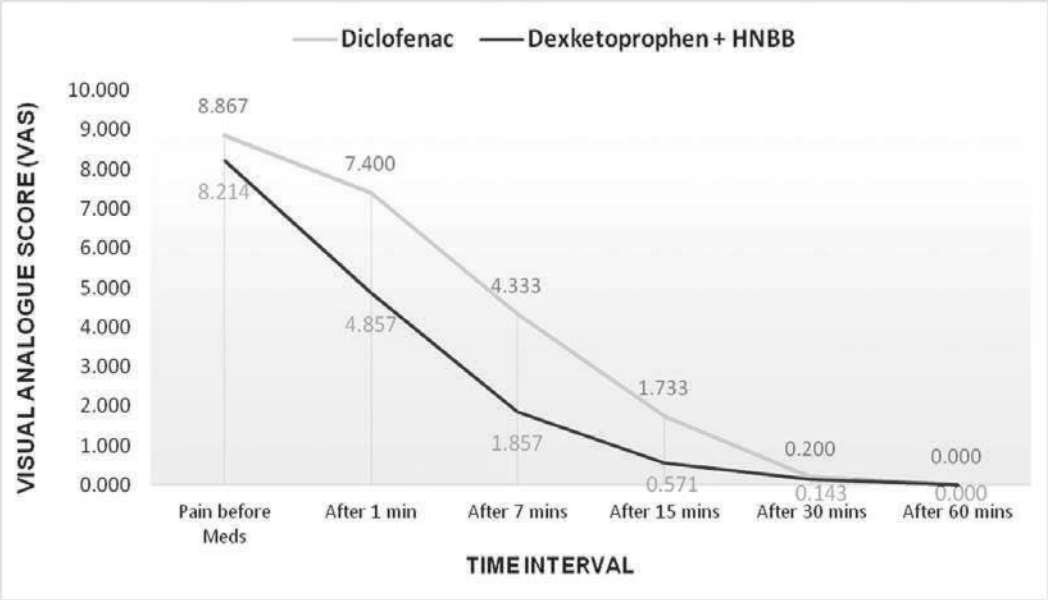

Figure 1. Change in visual analogue score given time interval and baseline pre-treatment score

Table 5. Before and after assessment results (Baseline and After 1, 7, 15, 30, and 60 minutes)

Type of Medicine	Test Statistics/ p-Value	Pre and Post Assessment per Time Interval				
		1 min - Pain before Meds	7 mins - Pain before Meds	15 mins - Pain before Meds	30mins - Pain before Meds	60mins - Pain before Meds
Diclofenac (n=15)	Z	-3.100[b]	-3.422[b]	-3.442[b]	-3.449[b]	-3.443[b]
	p-Value (2-tailed)	.002	.001	.001	.001	.001
Dexketoprophen + HNBB (n=14)	Z	-3.321b	-3.316b	-3.329b	-3.346b	-3.370b
	p-Value (2-tailed)	.001	.001	.001	.001	.001

a. Statistics: Wilcoxon Signed Ranks Test, Z (Before and After Test/Non-parametric Paired Samples T-Test)
b. Significance at p-value < 0.05

Table 6. Percent change from baseline and after 1, 7, 15, 30, and 60 minutes

Treatment Received	Percent Decrease				
	After 1 min	After 7 mins	After 15 mins	After 30 mins	After 60 mins
Diclofenac (n=15)	-17%	-51%	-80%	-98%	-100%
Dexketoprophen + HNBB (n=14)	-41%	-77%	-93%	-98%	-100%

Table 7. Test of significance on mean difference between diclofenac and combination of dexketoprophen + HNBB

Statistics/ p-value	Pain Before Meds	Time Interval 1 min	7 mins	15 mins	30mins	60mins
Mann-Whitney U	65.500	29.000	27.500	46.000	99.000	105.000
p-Value (2-tailed)	.067	.001	.001	.006	.620	1.000
p-Value (1-tailed)	.085[b]	.001	.000	.009	.813[b]	1.000[b]

a. Grouping Variable: Type of Medicine
b. Statistics: Mann-Whitney Test
c. Significance at p-value < 0.05

Table 8. Affect sizes for 1, 7, 15, 30, and 60 minutes

Treatment Received	Effect Size After 1 min	After 7 mins	After 15 mins	After 30 mins	After 60 mins
Diclofenac	-1.481	-7.388	-4.577	-7.394	-7.202
Dexketoprophen + HNBB	-4.187	-8.560	-7.929	-8.297	-9.532

Table 9. Standardized response means for 1, 7, 15, 30, and 60 minutes

Treatment Received	Standardized Response Mean After 1 min	After 7 mins	After 15 mins	After 30 mins	After 60 mins
Diclofenac	-0.947	-2.938	-6.134	-15.459	NA
Dexketoprophen + HNBB	-2.486	-4.070	-6.601	-15.100	NA

combination group had faster pain relief, which is after a minute, 41% improvement was observed versus 17% decline in pain among patients who took Diclofenac alone. At 30 and 60 minutes, no significant difference was observed.

All patients in both groups showed that the effect of treatment was achieved even after a minute although larger effect size values were observed on the Dexketoprophen + HNBB. Better responses were also observed on same group. (Tables 5-9)

Discussion

Diclofenac has been known to have significant effects in the pain management of acute renal colic. Prospective randomized controlled trials have proven that intake of Diclofenac alone would significantly reduce pain at 30 minutes with 50% drop in severity of pain.[8] In the case of this study, it seemed that patients responded better with duration of reduction effect already recorded after 7 minutes with 51% improvement.

At the onset of treatment, both groups were experiencing severe pain, averaging VAS 8.867 for diclofenac group and 8.214 for the Dexketoprophen + HNBB group. After a minute, patients in the first group had mean VAS of 7.4, which could be interpreted as experiencing severe pain while mean VAS of patients taking combination of pain medications had already shown significant reduction of pain to moderate level or mean VAS of 4.857. At 7 minute time interval from baseline mean VAS, patients taking diclofenac had lower pain reduction to 4.333 VAS

which could still be categorized as moderately in pain while patients in the second group had almost no more pain, VAS = 1.857. At 15 minutes, patients taking combination drugs experienced drastic pain relief with mean VAS of 0.571 while patients in diclofenac had mean VAS of 1.733.

This study revealed that drastic pain relief could be achieved at 15 minutes for both groups with significant emphasis on the superiority of the combination effect of Dexketoprophen + HNBB in terms of faster relief. Patients' responsiveness to the combination of Dexketoprophen + HNBB also showed significant superiority compared to patients who took Diclofenac alone. Severity of pain was significantly improved in the former group even as early as after 1 minute, reducing the pain by 47% and with significantly large responsiveness metrics.

It could also be taken into account that mean creatinine of patients taking diclofenac alone is significantly greater than those of patients who took the combination drug ($p=0.042<0.05$).

NSAIDs decrease prostaglandin release caused by increasing tension in the urinary tract walls that, in turn, causes ureteric spasm and concurrent pain. Dexketoprofen was found to show good tolerability when administered intravenously, as well as intramuscularly, similar to previously published studies.[14] Rapid analgesic effect was seen and no adverse drug-to-drug interaction with HNBB was observed.

The results of the present study show that Dexketoprofen in combination with HNBB appears to have synergistic effects, as the pair was able to achieve pain reduction faster as compared to Diclofenac alone. Both medications were administered intramuscularly with noted improvement in VAS scores as early as 1 minute. However, at the 30-minute mark, both drugs exhibited similar levels of efficacy in managing pain from renal colic.

Conclusion

The effectiveness of Diclofenac and the combination of Dexketoprofen and Hyoscine N-butyl bromide were measured in terms of change in mean VAS from baseline to a given time interval. After a minute, both groups exhibited improvement in pain reduction. Superiority of the combination of Dexketoprofen and Hyoscine N-butyl bromide over Diclofenac alone in terms of faster pain relief among patients with renal colic was established; 41% of the pain subsided versus the 17% on patients who took diclofenac alone. Superiority of the combination treatments was also statistically proven better than diclofenac group in terms of higher responsiveness coefficients (effect size and standardized response) (p-value < 0.05). Further, significant improvement in the Visual Analogue Score (VAS) scale was proven until 15 minutes from its initial intake. At 30 to 60 minutes, mean VAS difference between the two groups showed no statistically proven significance.

Based on the results, Dexketoprofen + HNBB proved to be superior to Diclofenac alone in the pain management of patients with renal colic when administered intramuscularly. The combination of NSAIDs and an antispasmodic could be used as an alternative pain control regimen for faster onset of relief for patients with similar conditions.

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