

Original Research Article

Efficacy of Combined Tramadol with Diclofenac in Comparison with Monotherapy Treatment Using Buscopan Diclofenac or Tramadol in Renal Pain Control

Hussein Oudah Al-Jasmawy Adel Ibraheem Muhi Ali Abdulhaleem Kadhim*
Hilla Teaching General Hospital, Hilla, IRAQ

*E-mail: aliabduhaleem@yahoo.ca

Accepted 31 August, 2015

Abstract

Acute renal colic is a severe painful event; drugs used to treat this condition include anticholinergics, opioid analgesics and nonsteroidal anti-inflammatory drugs.

To compare drug's efficacy in ureteric pain relief by using monotherapy including Buscopan 20 mg IV, Diclofenac Sodium 75 mg IM and Tramadol 50 mg IV, with a combination of 2 drugs including Tramadol plus Diclofenac.

160 patients (110 males and 50 females), 16 to 75 years of age, with moderate to severe renal pain were treated in emergency department of Hilla Teaching General Hospital and private clinics. Parameters were observed after 10, 30, 60, minutes and 2 hours of drugs treatment. Assessment of analgesic effect of the drugs was done by using Numerical Rating Scale (NRS). Drug side effects also observed.

Buscopan was the least effective drug in pain relief with higher side effects, while Diclofenac and Tramadol have comparable efficacy. Combination of Diclofenac plus Tramadol had a significant efficacy with rapid and sustained pain relief. Incidence of ureteric colic are more common in males than females (male to female ratio is 3/1).

For quick pain relief in acute renal colic, a combination of intravenous tramadol with diclofenac sodium is superior to each of them alone, while Buscopan is the least effective, with higher side effects.

Key words: Renal colic, Buscopan, Diclofenac sodium, Tramadol.

الخلاصة

المغص الكلوي الحاد هو حالة ألم شديد جداً. يستخدم لعلاج البسكوبان والادوية الافيونية ومضادات الالتهاب غير الستيرويدية. الهدف من هذه الدراسة هو مقارنة فعالية ٢٠ ملغ من البسكوبان و ٥٠ ملغ من الترامادول و ٧٥ ملغ من الديكلوفيناك بالإضافة الى استعمال الترامال والديكلوفيناك معاً. تمت معالجة ١٦٠ مريض ١١٠ رجال و ٥٠ نساء تتراوح اعمارهم بين ١٦ الى ٧٥ سنة يشكون من مغص كلوي متوسط الشدة ال شديد جداً في طوارئ مستشفى الحلة التعليمي العام والعيادات الخاصة. تمت مراقبة الاستجابة للعلاج بعد فترات ١٠- ٣٠- ٦٠ و ٢ ساعة بعد بدء العلاج. لوحظ ان النساء اقل اصابة من الرجال حوالي بنسبة ١ الى ٣. كما لوحظ ان البسكوبان اقل الادوية المستخدمة فعالية في تقليل الألم مع زيادة في الاعراض الجانبية في حين كان للترامال والفولتارين فعالية مقاربة. وتبين في استخدام الترامال و الديكلوفيناك مع الحصول على فعالية اسرع واكثر استدامة لذا نوصي ولسرعة تخفيف الألم المبرحة للمغص الكلوي استخدام الترامال الوريدي مع الديكلوفيناك العضلي وعدم استخدام البسكوبان لقلة فعاليته وكثرة اعراضه الجانبية.

Introduction

Acute renal pain is usually due to upper ureteric obstruction leading to increase intrapelvic pressure, and to increase tension in the wall of ureter and renal pelvis. Increasing intrapelvic pressure causes local stimulation for prostaglandin E2 synthesis. Prostaglandin E2, the most known powerful diuretic causes the subsequent vasodilation and induces a diuresis which further increases the intrapelvic pressure leading to the severe renal colic [1]. In addition to the above, prostaglandin acts directly on the ureter to induce spasm of the smooth muscles, and then the ureteric stone stimulate ureteric peristalsis in an attempt to move stone. Further narrowing of ureter occurred by oedema and inflammation when the stone lodged causing further ureteric spasm [2].

Severity of renal colic make the pain relief is the most important issue. The patient looks rolling and tries to change position seeking for relief. Some of drugs used to manage renal colic pain as NSAIDS and opioids are of comparable efficacy, while others as anti-spasmodic, diuretics and force diuresis are of debate value and even harmful. Regimen of over hydration has no advantage and may carry the risk of pelvic rupture with urine extravasation and infection. [3].

Antimuscarinic agents theoretically can be effective on ureteric peristaltic activity because it controlled by the autonomic nervous system [4]. Although the efficacy of these spasmolytic drugs in renal colic has been debated, they are still commonly used alone or as combinations with other drugs as Dipyron or opiates. The widely used one is hyoscine N-butyl bromide (Buscopan), which demonstrated low analgesic effects [5]. The obvious side effects of Buscopan as dry mucus membrane, photophobia, flushing and urine retention are the cause of its limited use [4].

NSAIDs have a potential effect on renal auto-regulatory response to urinary obstruction by decreasing a renal blood

flow, and reducing glomerular filtration rate up to 35% [7], it is generally well tolerated in healthy individuals, but not if there is pre-existing renal impairment or severe dehydration [8].

NSAIDs alone or combined with opioids are now the most commonly used drugs in ureteric colic, not only due to its analgesic effect but because it deals with the pathophysiology of renal pain. The analgesic effects of these drugs are by the inhibition of prostaglandin synthesis, preventing afferent vasodilation, decrease diuresis and intrapelvic pressure, so resulting in pain relief. NSAIDs also reduce oedema, inflammation and ureteric peristalsis [6].

Potent opioids as morphine or weak opioid as tramadol can be used as an alternative to diclofenac for patients who are at risk of NSAIDs side effects, as with impaired renal function, severe dehydration or in patients with history of peptic ulcer [9]. The narcotic semi-synthetic opiate, Tramadol is the best choice in these situations in spite of its side effects, that these side effects like nausea, vomiting, respiratory depression and dependence are less than with other opiates as morphine or pethidine. Hasher et al found that IM 100 mg tramadol is effective as 50 mg pethidine, nevertheless its effect in pain of renal colic need more evaluation. [10].

Drugs combination in renal colic management is used to obtain faster and better pain relief than monotherapy and to minimize the need for rescue analgesic dose. The common combinations used from the above three groups are Ketorolac with morphine [11], Diclofenac sodium with IV papaverine hydrochloride [12], hyoscine with dipyron (Buscopancompositum) [13], and IV opioids plus NSAIDs or acetaminophen [14].

Materials and Methods

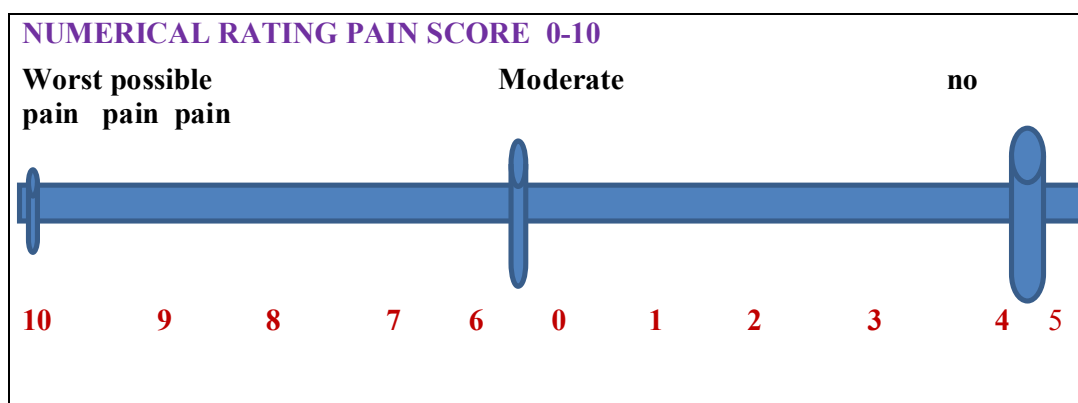
Patients with moderate to severe renal or ureteric colic were treated in emergency department of Hilla Teaching General

Hospital and in our private clinics. Exclusion criteria for this study included patients younger than 18 and older than 80, a known drug allergy to Diclofenac, Tramadol or Buscopan, history of peptic ulcer, asthma or renal failure, and pregnant or lactating mother. One-hundred sixty patients (100 males and 60 females) were included. Clinical assessment done for each patient includes full history, examination, ultrasound and general urine examination.

Patients were divided into four groups and they received treatment as : Group 1 received 20 mg IV Buscopan (Hyoscine

N-Butyl bromide), Group 2 received Diclofenac sodium 75 mg IM, Group 3 received 50mg Tramadol IV and Group 4 received Tramadol 50 mg IV plus 75 mg IM Diclofenac sodium.

Pain intensity and response to treatment were evaluated by asking the patients using a Numerical Rating Scales (NRS). In NRS we inform the patient to choose a number from 0 to 10 that best describes their status. Pain 0 equal to (No pain) and 10 would mean (Worse possible pain). We used the NRS scale shown below:



Numerical rating scale (NRS): NRS score were recorded for all the patients, and the mean score was calculated for each group, at baseline pain intensity consequently reported at 0 min, 10 min, 30 min, 60 min, and 2hour. Drugs side effects also reported during two hours of treatment. Random selection of patients in each 4 groups was done regardless their age, sex and pain intensity.

Results

The 160 studied patients considered of 110 men and 50 women with the overall mean age of 37.08 years (range, 16 to 75 years)(Table 1). Baseline characteristics, including age, sex and pain intensity at time of presentation show no significant difference between the four groups. Male is more common than female, male to female ratio is 3/1.

Table 2 summarizes the results of pain intensity among the four groups. NRS scale mean value were 8.50, 8.55, 8.65, 8.85 for Buscopan, Diclofenac, Tramadol, and Diclofenac plus Tramadol

respectively, so they were comparable for the entire groups at time of presentation (zero minute) ($p>0.05$). After 10 minutes of administration, significant decrease in mean NRS score was shown: 5.00 and 4.55 for group three and four respectively. After 30 and 60 minutes decrease in group two NRS score was observed (4.05). After 60 minute of drugs administration, comparable decrease in the NRS score, 2.55, 4.00, 2.00 for groups two, three and four respectively. The least decrease in NRS score noticed in Buscopan groups (5.5) after 2 hours from administration. Tramadol group showed starting increase in RNS score 4.00 and 4.50 after 60 minutes and 2 hours

respectively, which may necessitate another dose in some patients. Adding IV Tramadol from the start to IM Diclofenac gave the most quick and sustained pain relief that NRS score decrease to 4.55 after 10 minute and continue decreasing to 1.50 after 2 hours from drugs induction.

Table 3 shows the common drugs side effects for the four groups. Dry mouth, nausea, vomiting and skin rash was the common side effects of Buscopan while Nausea, vomiting and dizziness are the prominent side effects of Tramadol.

Table 1: Age and sex of the study patients

Group	Age range (years)	Mean age	Male	Female
1	16 to 75	40.20	30	10
2	19 to 74	38.25	25	15
3	16 to 68	32.35	26	14
4	18 to 72	37.50	29	11

Table 2: Mean NRS score at different intervals of the four groups

Group	Time interval				
	0 min	10 min	30 min	60 min	2 hours
1- Buscopan	8.50	8.30	6.00	5.55	5.50
2- Diclofenac	8.55	8.20	4.05	2.55	2.00
3- Tramadol	8.65	5.00	3.40	4.00	4.50
4- Diclof.+Tramadol	8.85	4.55	2.45	2.00	1.50
P value	> 0.05	<0.05	<0.05	<0.05	<0.05

Table 3: Drugs side effects of the four groups

Group	Side effects (Patients No.)					
	nausea	vomiting	dizziness	dry mouth	rash	urine retention
1-Buscopan	6	6	2	15	4	2
2-Diclofenac	1	2	1	0	0	0
3- Tramadol	10	8	4	0	0	1
4- Diclof.+Tramadol	8	9	5	1	0	0

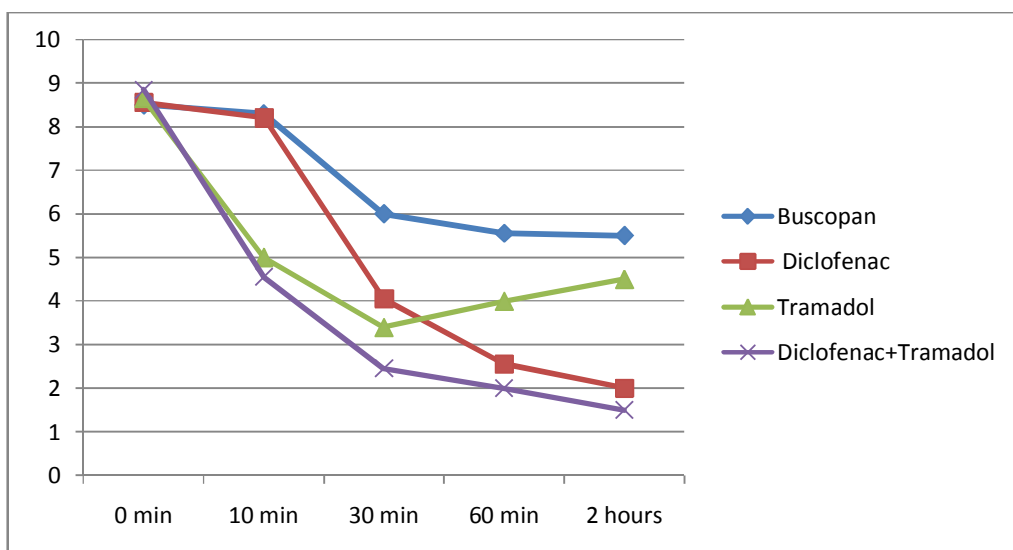


Figure 1: NRS score at different intervals of the three groups

Discussion

The pain of renal colic is very severe and may be worse than child birth or broken bone pain, for this reason the rapid and complete control of pain is regarded as the most important point in therapeutic approaches of renal colic treatment.

In this study the mean age incidence is (32.35 to 40.20 years), and male is more common than female (160 men and 50 women) (Table 1), this results is acceptable if we know that the incidence kidney stone disease in men is 2-3 times more common than women and more common in adult than elderly and least common in children [15].

The result of drug efficacy at different time intervals [Table2] reveal that the least decrease in pain score is with Buscopan group, and this is comparable with many studies of Buscopan analgesic effect as monotherapy in renal colic, in which they observe its inferiority to NSAIDs and opioids. In addition to that, there is no role of Buscopan in facilitating the passage of ureteric stones [16].

Diclofenac sodium and Tramadol are equally effective in decreasing pain

intensity and patients obtained significant pain relief at 30 minute. Tramadol group distinction is by starting clear improvement in pain intensity at only 10 minute [Figure 1]. In literatures, Cordell and et al found that NSAIDs and opioids have similar efficacy and there is no significant difference in decreasing pain intensity by 20-30 minute after administration [17].

Even with the singularity of Tramadol group, by rapid decrease in pain intensity which noticed only after 10 minute, the pain start to increase at 60 minute and two hour intervals [graph 2], that may necessitate another dose. Regarding the need for another doses, Hold gate and et al found that opioids even pethidine and morphine which is 6-10 times more potent than tramadol has greater like hood of further analgesia than with NSAIDs [18].

Drugs side effects are less with Diclofenac and higher in Buscopan groups (dry mouth, nausea, vomiting, and rash, while vomiting and dizziness are the common side effects with tramadol. Side effect of these drugs put NSAIDs as the first choice [19].

In this study, and after revision of most of trials studying pain management in renal colic we choose Diclofenac and Tramadol combination for many reasons: firstly Diclofenac is the most effective NSAIDs in relieving renal colic pain, because of its high analgesic effects and it deals with the pathophysiology of renal pain with less side effects than opioids or Buscopan [20]. Secondly Tramadol, the rapid acting opioid-like drugs is available in most of outpatient clinics, with fewer side effects than other opioids as morphine and pethidine which may cause vomiting, respiratory depression and dependency [21]. Thirdly the combination in many studies found to be better than monotherapy in obtaining a rapid and sustain pain relief, in addition to decreasing the need of rescue analgesia in general practice. An example of the increase in combination as in Australian centres, in a study found that the combination of IV narcotic (with or without adjuvant NSAID) was used in 3% of the patients in 1993 compared to 95% in 1997[22].

Finally we evade Buscopan from combination taking into consideration that a lot of articles against its use and an example of these are Holdage and et al who reported that there is no role of antispasmodics in renal colic pain treatment, and no evidence that the use of antispasmodic decrease the need of opioids [23]. As well as for each of the above, there are few published trials examining the potential synergistic effect of NSAIDs and opioids.

Conclusion

To obtain rapid and sustain pain relief in the treatment of acute renal colic, intravenous tramadol plus diclofenac sodium is superior to Buscopan and to either of tramadol or diclofenac alone. We recommend this treatment as a regimen, when there are no drugs contraindications and not to use anticholinergic drugs as Buscopan due to its poor analgesic effect and high side effects.

References

- 1- Anna Holdgate, Tamara Pollock. Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. *BMJ*. 2004 Jun 12; 328(7453): 1401.2- Crowley, A.R.; Byrne, J.C.; Darracott Vaughan, E.; Marion, D.N. The effect of acute obstruction on ureteral function. *J. Urol*. 1990;143:596–599.
- 3-Hess B. Medical management of acute renal colic - there is more than hydration and Buscopan. *Praxis (Bern 1994)*. 2011 Mar 2; 100(5):293-7.
- 4-Davenport K, Timoney AG, Keeley FX. Conventional and alternative methods for providing analgesia in renal colic. *BJU Int*. 2005; 95(3):297-300.
- 5- Lloret J, Munoz J, Monmany J, Puig X, Bonastre M, Brau J, Sola J, Domingo P, Jane F. Treatment of renal colic with dipyrrone. *Curr Ther Res* 1987; 42:1119-26.
- 6-Serinken M, Karcioğlu O, Turkcuer I, Ozkan HI, Keysan MK, Bukiran A. Analysis of clinical and demographic characteristics of patients presenting with renal colic in the emergency department. *BMC Res Notes*. 2008; 1:7.
- 7- Perlmutter, A.; Miller, L.; Trimble, L.A.; Marion, D.N.; Vaughan, E.D., Jr.; Felson, D. Toradol, an NSAID used for renal colic, decreases renal perfusion and ureteral pressure in a canine model of unilateral ureteral obstruction. *J. Urol*. 1993;149:926–930.
- 8-Lafrance J.P., Miller D.R. Selective and non-selective non-steroidal anti-inflammatory drugs and the risk of acute kidney injury. *Pharmacoepidemiol. Drug. Saf*. 2009; 18:923–931.
- 9-Bultitude M, Rees J. Management of renal colic. *BMJ* 2012; 345: e 5499.
- 10- Hazhir S, Ahmadi YA, Darabi JN. Intramuscular Tramadol versus Intramuscular Pethidine for Treatment of Acute Renal Colic. *Urol J* 2010; 7:148-51.
- 11-Ghuman J, Vadera R. Ketorolac and morphine for analgesia in acute renal colic: is this combination more effective

- than monotherapy? CJEM. 2008 Jan; 10(1):66-8.
- 12-Asgari, S. A., Asli, M. M., Madani, A. H., Maghsoudi, P. A., Ghanaei, M. M., Shakiba, M., Aval, H. B., Enshaei, A., Farzan, A. and Esmaeili, S. (2012), Treatment of loin pain suspected to be renal colic with papaverine hydrochloride: a prospective double-blind randomised study. BJU International, 110: 449–452. doi: 10.1111/j.1464-410X.2011.10793.x. Epub 2012 Feb 20.
- 13- W. Oosterlinck, W.DeSy. A double-blind comparison between meptazinol (Wy22811) and 'Buscopan' Compositum in renal colic Current Medical Research & Opinion 1976 3:10, 716-718.
- 14- F, Eken C, Karadeniz O, Goksu E, Cubuk M, Cete Y. Intravenous Paracetamol or Morphine for the Treatment of Renal Colic: A Randomized, Placebo-Controlled Trial. Ann Emerg Med. 2009; 54:568-574.
- 15- Portis AJ CP. Diagnosis and initial management of kidney stones, Sundaram. Am Fam Physician. 2001; 63(7):1329-38.
- 16- Papadopoulos G, Bourdounis A, Kachrilas S, Bach C, Buchholz N, Masood J, Hyoscine N-Butyl bromide (Buscopan®) in the Treatment of Acute Ureteral Colic: What Is the Evidence? Urol Int 2014; 92:253-257.
17. Cordell, W.H.; Larson, T.A.; Lingeman, J.E.; Nelson, D.R.; Woods, J.R.; Burns, L.B.; Klee, L.W. Indomethacin suppositories versus intravenous titrated morphine for the treatment of ureteral colic. Ann. Emerg. Med. 1994, 23, 262–269.
- 18- Holdgate A, Pollock T. Nonsteroidal anti-inflammatory drugs (NSAIDs) versus opioids for acute renal colic. Cochrane Database of Systematic Reviews 2004, Issue 1. [DOI: 10.1002/14651858.CD004137.pub2]
- 19- Labrecque M, Dostaler LP, Rousselle R, et al. Efficacy of nonsteroidal anti-inflammatory drugs in the treatment of acute renal colic. A meta-analysis [see comments]. Arch intern Med 1994; 154:1381–7.
- 20- Cole RS, Fry CH, Shuttleworth KE. The action of the prostaglandins on isolated human ureteric smooth muscle. Br J Urol 1988; 61:19.
21. Davenport K, Timoney AG, Keeley FX. Conventional and alternative methods for providing analgesia in renal colic. BJU Int. 2005; 95(3):297-300.
- 22-Kelly AM1. Nurse-managed analgesia for renal colic pain in the emergency department. Aust Health Rev. 2000; 23(2):185-9.
- 23- Holdgate A, Oh CM. Is there a role for antimuscarinics in renal colic? A randomized controlled trial. J Urol 2005; 174:572-5.