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Brief Report

Phloroglucinol as an adjuvant analgesic to treat renal colic

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Abstract

Purpose: We tested whether the addition of phloroglucinol to piroxicam could improve pain relief in patients with acute renal colic visiting the emergency department.

Materials and Methods: Patients with a diagnosis of acute renal colic were prospectively randomized to receive intravenous phloroglucinol (200 mg) or placebo combined with intramuscular piroxicam (20 mg). We monitored the visual analogic scale (VAS), heart rate, arterial blood pressure, need for rescue therapy, and adverse events at different time points for 1 hour. We recorded admission requirement and new visit at 72 hours for renal colic. The primary end point was to assess pain relief at 1 hour, defined as a decrease of 50% or more as compared with the initial VAS. The secondary objectives were to compare the 2 groups for VAS at any time points, the need for rescue therapy, and the occurrence of adverse events.

Results: Of the 309 eligible patients, 253 entered the study. A total of 126 patients received phloroglucinol and 127 patients received placebo. Pain relief at 1 hour was obtained in 89 patients (71%) receiving phloroglucinol and 89 patients (70%) receiving placebo ($P = .89$). There were no differences in VAS between the 2 groups at any time points. Rescue therapy was required in 37 patients (29%) receiving phloroglucinol and 38 patients (30%) receiving placebo ($P = .51$). Number of adverse events was similar with phloroglucinol and placebo: 20 (16%) and 16 (13%), respectively ($P = .44$).

Conclusions: There was no evidence that the addition of phloroglucinol improved the efficiency of piroxicam to relieve pain in acute renal colic.

1. Introduction

Renal colic is responsible for an acute pain related to the migration of calculi along the urinary tract. Pain related to renal colic is often reported as the more intense that patients can experience. A precocious and efficient pain management is therefore mandatory to treat this usually mild disorder. Pain related to renal colic is believed to result from the

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obstruction of the urinary tract, leading to an increase in intraluminal pressure. The overpressure stimulates the local release of prostaglandins that, in turn, leads to vasodilatation, diuresis, and ureteral spasm. These latter mechanisms are responsible for an even greater pressure that increases pain [1]. Recommendations suggest the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as standard analgesics for renal colic and of opioids as rescue medications [2]. It has been advocated for years that spasmolytic agents could efficiently participate in treatment of renal colic as they theoretically help relieve pain by smooth muscle relaxation [3]. Consequently, they are frequently used in daily practice [4]. However, because literature lacks evidence to support this strategy, latest recommendations do not endorse the use of spasmolytic agents in treatment of renal colic [5]. Phloroglucinol, a potent, well-tolerated antimuscarinic drug, is believed to relieve pain, thanks to its spasmolytic properties. Consequently, phloroglucinol has legal approval and is routinely used as an adjuvant treatment of renal colic.

To our knowledge, no study has reported the efficacy of phloroglucinol to relieve pain related to renal colic. Therefore, we aimed to evaluate the efficacy and tolerance of phloroglucinol associated to NSAID in patients visiting the emergency department for renal colic.

2. Patients and methods

2.1. Participants

We conducted a monocenter, prospective, interventional, double-blind study in the emergency department of a tertiary teaching hospital (Monastir, Tunisia) attending to nearly 65 000 patients a year. We enrolled patients suspected to have renal colic. Board-certified emergency physicians attended patients around the clock.

Standardized screening forms were used to help identify eligible patients. We enrolled all consecutive consenting patients (≥16 years) presenting clinical symptoms and signs of renal colic. Diagnosis criteria were a history of unilateral colicky acute flank pain with urinalysis or ultrasonography findings consistent with the diagnosis of renal colic. Only patients displaying at least a visual analogical scale (VAS) of 30/100 or greater were included. Patients could not be included if they had a previous history of peptic ulcer disease, asthma, bleeding disorder (including the use of oral anticoagulant), impaired renal or hepatic function, or known hypersensitivity to aspirin, NSAIDs, or phloroglucinol and if they were pregnant and breast-feeding women. Patients could not be included if they had received painkillers within 6 hours before presentation. Study protocol and procedures complied with the principles of the Declaration of Helsinki. The institutional review board for the protection of human subjects of the institution approved the study protocol and patients' informed consent procedures. All enrolled patients provided informed consent for participation.

2.2. Intervention

After the patient agreed to enter the study, the investigator opened a sealed envelope and assigned the patient to the designated group. The sealed envelopes were opened in numerical order such that the first patient was assigned the treatment designated in the first envelope and the second patient was assigned the treatment designated in the second envelope, and so on. Sealed random code envelopes were not opened until the time of patient enrollment. Once the treatment assignment had been revealed by opening the sealed random code envelope, the patient was considered to be enrolled as a subject in the study. After randomization, patients received piroxicam (20 mg intramuscularly) as standard analgesic, with either phloroglucinol (200 mg in 20 mL of serum saline intravenously, 20 minutes) or placebo (20 mL of serum saline intravenously, 20 minutes) corresponding to the phloroglucinol and placebo groups, respectively. Rescue therapy was defined as the need for intravenous morphine titration if VAS at 60 minutes was above 50% the initial VAS or if VAS was above 50/100 at 2 successive time points.

2.3. Study outcomes

Level of pain was autoreported using the VAS. Heart rate, arterial blood pressure, and VAS were recorded before treatment initiation and sequentially at 5, 10, 15, 30, 45, and 60 minutes. Patients were systematically screened for the following adverse events: allergy (rash, edema, and bronchospasm), vomiting, headache, and palpitation. The primary end point was pain relief at 60 minutes, defined as a decrease in VAS of 50% or more as compared with the initial value.

The secondary end points were differences in VAS at any time course (5, 10, 15, 30, 45, and 60 minutes), need for rescue medication, and occurrence of adverse effects.

2.4. Statistical analysis

The sample size calculation was based on the hypothesis of a successful treatment with NSAID in 80% of patients. A minimum of 200 patients was required to detect a 10% absolute improvement of pain relief at 1 hour between the 2 groups with a power of 80% at the 2-sided α error of .05.

Differences of VAS in the 2 groups were compared using 1-way analysis of variance. Student t test and Fisher exact test were used to compare continuous and categorical variables, as required. P value below .05 was considered statistically significant.

3. Results

Participants were recruited from January to December 2004. Among 309 patients assessed for eligibility, 56 could not participate. The remaining 253 comprised the study

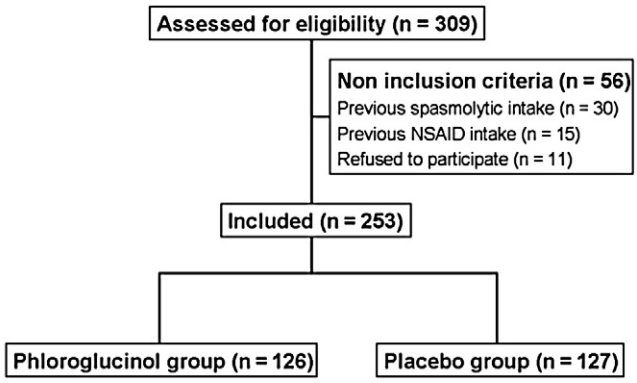

Fig. 1 Flowchart of patients screened for the study.

population; 126 were assigned to the phloroglucinol group and 127 were assigned to the placebo group (for details, see Fig. 1). The baseline characteristics of each group were comparable (Table 1). Five patients were admitted after visiting the emergency department: 1 had oligoanuria and 4 suffered from intense pain requiring ureteral catheterization. Only 7 patients revisited the emergency department within 72 hours because of recurrent renal colic. These issues were not influenced by the treatment groups.

Table 1 Baseline characteristics of patients according to treatment group

	Placebo group (n = 127)	Phloroglucinol group (n = 126)	*P*
Age (y), mean (SD)	39 (14)	35 (13)	.046
Sex (male), n (%)	72 (57)	66 (52)	.529
Previous renal colic, n (%)	62 (49)	66 (52)	.886
Previous ureteral calculi, n (%)	34 (27)	32 (25)	.616
Previous renal failure, n (%)	4 (3)	0 (0)	.122
Previous urogenital abnormalities, n (%)	2 (2)	2 (2)	1
Diabetes mellitus, n (%)	5 (4)	4 (3)	1
Delay from symptoms to ED referral (h), mean (SD)	30.6 (12)	16.8 (6)	.304
Baseline VAS, mean (SD)	74 (15)	73 (11)	.416
Temperature (°C), mean (SD)	37.1 (0.3)	37.1 (0.3)	.808
Blood pressure (mm Hg), mean (SD)			
Systolic	130 (17)	125 (17)	.153
Diastolic	76 (12)	78 (11)	.668
Heart rate (beats/min), mean (SD)	77 (9)	76 (18)	.385
Admission, n (%)	1 (1)	4 (3)	.213
New visit at 72 h for renal colic, n (%)	2 (2)	5 (4)	.447

Results are expressed as absolute no. (%) or mean (SD) as required. *P* value below .05 was statistically significant.

Table 2 Assessment of primary and secondary end points according to treatment group

	Placebo group (n = 127)	Phloroglucinol group (n = 126)	*P*
Pain relief at 1 h, n (%)	89 (70)	89 (71)	.89
VAS along time course (SD)			
5 min	70 (1.6)	72 (1.7)	.377
10 min	64 (1.9)	64 (2)	.947
15 min	56 (2)	57 (2)	.66
30 min	41 (2.3)	39 (2.5)	.568
45 min	35 (2.3)	33 (2.5)	.428
60 min	30 (2.3)	28 (2.5)	.633
Need for rescue medication, n (%)	38 (30)	37 (29)	.51
Adverse event, n (%)	16 (13)	20 (16)	.44
Rash	2 (2)	0 (0)	.49
Nausea, vomiting	9 (7)	10 (8)	.81
Headache	3 (2)	7 (6)	.21
Palpitation	2 (2)	3 (2)	.68

Results are expressed as absolute no. (%) or mean (SD) as required. *P* value below .05 was statistically significant.

Baseline VAS was 74 (SD 15) and 76 (SD 18) in the placebo and phloroglucinol groups, respectively. The kinetics of VAS were similar in the 2 groups, with a nonsignificant trend to improvement in the phloroglucinol group at 45 and 60 minutes (Table 2). No differences were notified for level of pain at 60 minutes. Finally, pain relief at 1 hour was obtained in 89 patients (71%) in the phloroglucinol group and 89 patients (70%) in the placebo group, and this difference was not statistically significant ($P = .89$). Arterial blood pressure and heart rate remained unchanged in both groups along the 1-hour evaluation.

Rescue therapy was required in a similar ratio in both groups. In addition, the occurrence of adverse events did not differ in patients who received phloroglucinol or placebo.

4. Discussion

Our results suggest that the use of phloroglucinol combined with NSAID is not deleterious but does not improve pain relief at 1 hour, the delay to pain relief, and the requirement for rescue therapy in patients visiting the emergency department for renal colic.

Although it is methodologically robust, we acknowledge that this trial has several weaknesses. Some guidelines recommend intravenous infusion of NSAID as a first-line therapy to relieve pain in renal colic [6]. The use of intramuscular NSAID may therefore be considered as a violation. However, meta-analyses [2,7] have studied the use of NSAID and proved that both intramuscular and intravenous use could be efficient. Of note, studies included in these meta-analyses mainly used intramuscular NSAID. In addition, recent studies on this topic efficiently used intramuscular

NSAID as first-line analgesics in renal colic [8]. Another weakness of our study is the lack of definitive diagnosis of renal calculi although participants had a clear clinical presentation of renal colic supported by urinalysis. In a recent interventional study, computed tomography scan failed to reveal kidney stones in 25 (15%) of 163 patients enrolled with a clinically suspected renal colic [9]. Therefore, we cannot rule out the hypothesis that the lack of response to antispasmodic agents was related to the absence of renal calculi.

We did not assess whether phloroglucinol could efficiently relieve pain in patients with renal colic if used as a single therapy. Drotaverine, a spasmolytic agent, has been previously tested to treat pain related to renal colic in a large interventional, multicenter, controlled study. In this study, drotaverine relieved pain in 79% of patients vs 46% of patients in the placebo group, with a limited toxicity [10]. An open label assay has compared intravenous ketorolac to sublingual hyoscyamine, an anticholinergic agent. This study resulted in a clear superiority of intravenous NSAID, whereas hyocyamine partially relieved pain [11]. Combining the 2 molecules did not improve the efficacy of NSAID in a randomized multicenter controlled trial [12]. It has been also demonstrated that adding hyoscine butylbromide to morphine and indomethacin did not reduce the subsequent requirement of morphine [9]. Recently, a study reported that papaverine hydrochloride was as efficient as diclofenac in relieving pain related to acute renal colic, whereas a combination of these 2 drugs did not improve pain relief [13]. This study concluded that using papaverine could reliably replace NSAIDs if these latter were contraindicated. Altogether, these results suggest that spasmolytic agents may help to relieve pain in patients with renal colic although their efficacy is probably inferior to that of NSAID. Unfortunately, our study did not bring any insight regarding the use of spasmolytic agents alone. In addition, combining NSAID and spasmolytic agents seems nonbeneficial on short-term outcome as level of pain and requirement of morphine are not improved by combination strategies [9]. We observed a nonsignificant trend to improvement of pain at 45 and 60 minutes, like the trial testing papaverine that reported a nonsignificant decrease in VAS at 40 minutes in the combination group. Consequently, it could be suggested that prolonged use of phloroglucinol could finally have an impact on pain relief. Interestingly, phloroglucinol seemed to improve ureteral expulsion of calculi [8]. Unfortunately, pain relief was not strictly monitored in this study, but patients who received phloroglucinol had no decrease in requirement of NSAID. Therefore, no evidence supports that phloroglucinol can have an impact on duration of pain. Consequently, trials failed to demonstrate a superiority of a strategy combining NSAID and phloroglucinol to relieve pain.

To summarize, our study suggest that phloroglucinol should not be added to NSAID as a first line treatment of pain related to renal colic.

References

[1] Shokeir AA. Renal colic: pathophysiology, diagnosis and treatment. Eur Urol 2001;39:241-9.

[2] Holdgate A, Pollock T. Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. Cochrane Database Syst Rev 2005;2:CD004137.

[3] Davenport K, Timoney AG, Keeley FX. Conventional and alternative methods for providing analgesia in renal colic. BJU Int 2005;95: 297-300.

[4] Engeler D, Schmid S, Schmid HP. The ideal analgesic treatment for acute renal colic: theory and practice. Scand J Urol Nephrol 2008;42:137-42.

[5] Tiselius HG, Ackermann D, Alken P, Buck C, Conort P, Gallucci M. Guidelines on urolithiasis. http://www.uroweb.org/fileadmin/tx_eauguidelines/Urolithiasis.pdf.

[6] Anonymous. Management of renal colic in the emergency department. http://www.sfmu.org/documents/consensus/cc_cna_long.pdf.

[7] Labrecque M, Dostaler LP, Rousselle R, Nguyen T, Poirier S. Efficacy of nonsteroidal anti-inflammatory drugs in the treatment of acute renal colic. A meta-analysis. Arch Intern Med 1994;154:1381-7.

[8] Dellabella M, Milanese G, Muzzonigro G. Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. J Urol 2005;174:167-72.

[9] Holdgate A, Oh CM. Is there a role for antimuscarinics in renal colic? A randomized controlled trial. J Urol 2005;174:572-5.

[10] Romics I, Molnár DL, Timberg G, Mrklic B, Jelakovic B, Köszegi G, et al. The effect of drotaverine hydrochloride in acute colicky pain caused by renal and ureteric stones. BJU Int 2003;92:92-6.

[11] Jones JB, Dula DJ. The efficacy of sublingual hyoscyamine sulfate and intravenous ketorolac tromethamine in the relief of ureteral colic. Am J Emerg Med 1998;16:557-9.

[12] Jones JB, Giles BK, Brizendine EJ, Cordell WH. Sublingual hyoscyamine sulfate in combination with ketorolac tromethamine for ureteral colic: a randomized, double-blind, controlled trial. Ann Emerg Med 2001;37:141-6.

[13] Snir N, Moskovitz B, Nativ O, Margel D, Sandovski U, Sulkes J, et al. Papaverine hydrochloride for the treatment of renal colic: an old drug revisited. A prospective, randomized study. J Urol 2008;179:1411-4.