



Review

Neostigmine for acute colonic pseudo-obstruction: A meta-analysis

Raul Guillermo Lopez Valle^{*,1}, Francisco Lopez Godoy¹

San Jacinto Methodist Hospital Family Medicine Residency Program, Baytown, TX, USA

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ABSTRACT

Introduction: Acute colonic pseudo-obstruction (ACPO) is an uncommon condition that occasionally develops in hospitalized patients with serious underlying ailments. Its early recognition is essential to reduce life-threatening complications. Few low-powered randomized clinical trials (RCTs) have confirmed the effectiveness of neostigmine for treatment.

Aim: To analyse the effectiveness and main side effects of neostigmine in the treatment of ACPO.

Experimental: A literature search was performed for all published RCTs, reporting on neostigmine as treatment for ACPO.

Results: Four studies fulfilled the inclusion criteria, evaluating 127 patients: treatment group = 65, control group = 62. Neostigmine effectiveness to resolve ACPO with only one dose was 89.2% versus 14.65% ($P < 0.001$, NNT = 1 [95% CI 1–2]).

Conclusions: Neostigmine is a safe and effective option for patients with ACPO who failed to respond to conservative management.

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1. Background

Acute colonic pseudo-obstruction (ACPO), also known as Ogilvie syndrome, is the gross dilatation of the colon without mechanical obstruction [1–6]. It mostly occurs in elderly patients with associated medical or surgical conditions [4–8], like cardiovascular, neurological, obstetric, infectious or inflammatory, metabolic, respiratory, post-traumatic, post-surgical and pharmacological insults [3–5,7,9]. It is a rare condition, occurring in 0.046% of patients after coronary bypass grafting [8]; in 0.29% of burn patients [10], and in 0.29–1.3% of patients after hip, knee arthroplasty or spinal surgery [11,12].

Its aetiology is still unknown [3,5]. The accurate diagnosis remains difficult and it is based upon clinical and radiographic findings [1,3–5]. It is early recognition and management are essential to reduce life-threatening complications, like colonic ischaemia and perforation, and to improve outcome [1–5,7,9]. Once diagnosed, the traditional management is conservative, including gastric decompression, fluid and electrolyte balance correction, rectal tube decompression, limiting offending drugs and the diligent treatment of any underlying condition [3–7,13], which is usually given for 48–72 h [3,5,7] if there is not right iliac fossa tenderness and/or

grossly dilatation of the caecum [3]. Nonetheless, many anecdotal reports confirmed the effectiveness of neostigmine for treatment of ACPO, which promoted the interest in the pharmacological treatment of this ailment [3,6]. Furthermore, there are few low-powered randomized clinical trials (RCTs) that have analysed its usefulness [2,14]. To our understanding, only two systematic reviews have evaluated the effectiveness of neostigmine for the treatment of ACPO [2,9], however, none of them performed a meta-analytic approach to fully provide consistent evidence. Our aim was to analyse the effectiveness and main side effects of neostigmine in the treatment of ACPO through a meta-analytic approach of available RCTs.

2. Methodology

A literature search was performed using Embase, Medline, Cochrane, and Pubmed databases, using Boolean logic and the keywords “neostigmine”, “acute colonic pseudo-obstruction” and “Ogilvie syndrome”. Only RCTs were searched, without imposing language, publication date or publication status. Two reviewers independently extracted the data and any discrepancies about inclusion of studies and/or interpretation of data were resolved by arbitration and consensus. Further information was retrieved through manual search of references from recent reviews or published original studies. We performed the same approach directly on Google (search engine), following the same lineaments. The demographic information extracted from each study

* Corresponding author. Affinity Medical Associates, 11550 Louetta Suite 1200, Houston, TX 77070, USA. Tel.: +1 281 320 1196; fax: +1 281 320 1209.

E-mail address: memovallemd@yahoo.com (R.G.L. Valle).

¹ Diplomate American Board Family Medicine.

was first author, publication year, demographics, study design, and number of subjects (Table 1), clinical response in each group and complication rates were measured and tabulated (Table 2). The quality of each trial was assessed using the Jadad score [15] and the CONSORT Statement [16]. The statistical analysis was only done for clinical response and main side effects. For categorical variables the Peto odds ratio was used as the summary statistic. Statistical analysis was done with Comprehensive Meta-Analyst (ver 2.2.0). Results were translated into clinical outcome benefits by calculating the number needed to treat (NNT), which were calculated as the inverse of the absolute risk reduction (the difference between the control event rate minus the experimental event rate) for each study, rounding up to the nearest whole number. The same procedure was used to calculate the number needed to harm (NNH).

3. Results

Fig. 1 summarises the selection of studies. Four RCTs were found [17–20]. Table 1 depicts the general information of those RCTs included. The number of patients included in each one ranged from 21 to 42, totalling 127 patients, divided in two groups: 65 in the treatment group (51.2%) and 62 in the control group (48.8%). The average age ranged from 64 to 66.7 years. The male:female ratio was 1.7:1. Only three studies used the intravenous route (dose ranged from 2.0 to 5 mg) and the administration time ranged from 3 min to 12 h. Only one article used the nasal route, with a total dose of 24 mg, equivalent to 0.55 mg IV [21]. Tables 2 and 3 show the main results, as follow:

- 1) Neostigmine effectiveness to resolve ACPO with only one dose averaged was 89.2% (ranging from 84.6 to 95.2%) versus 14.8% (from 0.0 to 45.0%) of control group (NNT = 1 [95% CI 1–2]).
- 2) Size effects:
 - a) Abdominal pain was the most common side effect, occurring in 53.1% (42.9–72.7%, OR = 17.4 [IC 95% 5.3–57.2], NNH = 2 [95% CI 1–3]).

- b) Sialorrhoea was the second most common side effect, occurring in 31.1% (23.1–38.1%, OR = 9.4 [IC 95% 3.0–29.2], NNH = 3 [95% CI 2–6]).
- c) Vomiting was the next most common side effect, seen in 15.6% (9.1–19.1%, OR = 7.5 [IC 95% 1.2–48.8], NNH = 5 [95% CI 3–375]).
- d) Bradycardia appeared in 6.3% (4.8–9.1%, OR = 6.3 [IC 95% 0.3–102], NNH = 16 [95% CI 6–25]). A consideration is that, even though the OR > 1, the lower limit of the confidence interval spanned below 1, therefore, this is not significant, because of the very few cases included.

There was substantial heterogeneity in the included studies (I^2 index = 63.34%), probably because the differences were more related to study design (small number of RCTs or high response in the control arm of the study of Orlando) rather than chance. When the study of Orlando was removed from the analysis, the effectiveness of neostigmine for ACPO resolution was 95.6% versus 0.00% in the control group, (NNT = 1 [95% CI 1–1], $Z = 8.757$, $P < 0.001$, $Q = 0.113$, $I^2 = 0.000$, $\tau^2 = 0.000$). But it is important to state that a funnel plot representation with only four studies is not appropriate, because the power of the test is too low to able to discriminate chance from real asymmetry.

4. Discussion

ACPO is still a poorly understood entity with an aetiology attributed to an autonomic imbalance between the sympathetic and parasympathetic innervation of the colon [5,22], which leads to inhibition of peristalsis [22], due to either sympathetic stimulation or parasympathetic suppression [4,5,9]. Trevisani concluded that the most plausible aetiology of ACPO was because of parasympathetic suppression, and not by sympathetic over-activity [23] and this seems to be the current pathophysiological explanation [4,7].

Neostigmine, a parasympathomimetic agent that reversibly inhibits acetylcholine hydrolysis by competing with acetylcholinesterase at sites where cholinergic transmission occurs [3–5,7,19,24],

Table 1
Selected randomized controlled trials evaluating the effect of neostigmine in ACPO.

Author	Year	N	Age ^a	b	c	Conditions/patients	Dose ^d	Jadad ^e	Consort ^f
Orlando	1994	40		16	24	Cholecystectomy: 20 Emergency surgery: 20	24 mg, nasal puff 6%	4	20
Ponac	1999	21	65.5	19	2	Recent surgery: 11 Medical condition: 10	2 mg/3–5 min	4	20
von der Spoel	2001	24	69.7			Cardiac surgery: 10 Infectious illness: 7 Cardiac illness: 4 Gastroenterological illness: 1 Gastroenterological surgery: 1 Vascular surgery 1	5 mg/50 mL NS @ 4 mL/h	4	27
Fanaei	2008	42	64	30	12	Prostatectomy: 11 patients Laparoscopic appendectomy: 10 Laparoscopic cholecystectomy: 8 Total knee replacement: 5 Hip replacement: 3 Foot amputation: 2 Lumbar laminectomy: 1 Exploratory laparotomy: 1 Open reduction/fixation of fracture: 1	2/5 mg in 500 mL NS/30 min	1	17
		127		65	38				

^a Reported as mean (years).

^b Male.

^c Female.

^d Dose and administration route.

^e Ref. 15.

^f Ref. 16.

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