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ORIGINAL ARTICLE

Comparison of posterior internal anal sphincter myectomy and intrasphincteric botulinum toxin injection for treatment of internal anal sphincter achalasia: a meta-analysis

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Abstract
Purpose Internal anal sphincter (IAS) achalasia is a clinical condition with presentation similar to Hirschsprung's disease, but with the presence of ganglion cells on rectal suction biopsy (RSB). The diagnosis is made by anorectal manometry (ARM), which demonstrates the absence of the rectosphincteric reflex on rectal balloon inflation. The recommended treatment of choice is posterior IAS myectomy. Recently, intrasphincteric botulinum toxin (Botox) injection has been effectively used for treatment of IAS achalasia. The aim of this meta-analysis was to compare the efficacy of posterior IAS myectomy with intrasphincteric Botox injection for treatment of IAS achalasia.
Methods A systematic literature search for relevant articles was conducted using the following databases: MEDLINE®, EMBASE®, ISI Web of Science℠ and the Cochrane Library. A meta-analysis was performed with the studies where IAS achalasia was diagnosed based on the results of ARM and RSB. Odds ratio (OR) with 95 % confidence intervals were calculated.
Result Sixteen prospective and retrospective studies, published from 1973 to 2009, were identified. A total of 395 patients with IAS achalasia were included in this meta-analysis. Fifty-eight percent of patients underwent IAS myectomy and 42 % Botox injection. Regular bowel movements were significantly more frequent after IAS myectomy (OR 0.53, [95 % CI 0.29–0.99]; $p = 0.04$). There was no significant difference in continued use of laxatives or rectal enemas (OR 0.92, [95 % CI 0.34–2.53], $p = 0.89$) and in overall complication rates between both procedures (OR 0.68, [95 % CI 0.38–1.21]; $p = 0.19$). Looking at specific complications, the rate of transient faecal incontinence was significantly higher after Botox injection (OR 0.07, [95 % CI 0.01–0.54]; $p < 0.01$). Constipation and soiling were not significantly different between both procedures (OR 0.66, [95 % CI 0.30–1.48]; $p = 0.31$ and OR 0.24, [95 % CI 0.03–2.07]; $p = 0.25$). The rate of non-response was significantly higher after Botox injection (OR 0.52, [95 % CI 0.27–0.99]; $p = 0.04$). Subsequent surgical treatment was significantly more frequent after Botox injection (OR 0.18, [95 % CI 0.07–0.44]; $p < 0.0001$). Short- and long-term improvements were significantly more frequent after IAS myectomy (OR 0.56, [95 % CI 0.32–0.97]; $p = 0.04$ and OR 0.25, [95 % CI 0.15–0.41]; $p < 0.0001$).
Conclusion This meta-analysis indicates that in patients with IAS achalasia, posterior IAS myectomy appears to be a more effective treatment option compared to intrasphincteric Botox injection. After Botox injection, the rate of transient faecal incontinence, non-response and subsequent surgical procedures were significantly higher compared to IAS myectomy.

Keywords Internal anal sphincter achalasia · Internal anal sphincter myectomy · Botulinum toxin injection · Meta-analysis

Introduction

Internal anal sphincter (IAS) achalasia is a condition with clinical presentation similar to Hirschsprung's disease [1–4]. The IAS is a specialized smooth muscle continuation of the circular muscle layer of the rectum, which plays a significant role in the maintenance of anorectal continence [5].

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The exact pathogenesis and pathophysiology of IAS achalasia is still not fully understood. Several enzyme- and immunohistochemical studies [6–10] have shown altered intramuscular innervations in the IAS of patients with IAS achalasia. Absence of nitrergic innervations within the IAS muscle in patients with IAS achalasia is believed to be responsible for the motility dysfunction in these patients. Because nitrergic nerves regulate smooth muscle relaxation, their deficiency or absence in patients with IAS achalasia has been suggested to be responsible for spasm or increased tone in the IAS in these patients [7]. The IAS relaxes in response to rectal distension, a phenomenon called the rectosphincteric inhibitory reflex, which is mediated by intramural nerves descending from the rectum to the IAS [5]. The IAS receives adrenergic, cholinergic and nonadrenergic noncholinergic (NANC) innervations [7]. It has been reported that IAS relaxation is brought about by the activation of intramural NANC nerves. Nitric oxide is now recognized as a potent mediator of NANC inhibitory nerves, which regulate smooth muscle relaxation in the mammalian gastrointestinal tract, including IAS [11].

The failure of relaxation of the IAS is the causative factor for severe constipation with or without soiling in patients with IAS achalasia [12]. The diagnosis of IAS achalasia is based on (1) anorectal manometry (ARM), which demonstrates the absence of rectosphincteric inhibitory reflex on rectal balloon inflation and the presence of marked rhythmic activity of the IAS (Fig. 1), and (2) rectal suction biopsy (RSB), which shows the presence of ganglion cells and normal acetycholinesterase activity [13].

Posterior IAS myectomy has been recommended as the treatment of choice for patients with IAS achalasia [14–16]. Recently, the use of intrasphincteric botulinum toxin (Botox) injection has been effectively used as a therapeutic alternative in the management of these patients [17–19]. Several long-term studies have been published evaluating both procedures with inconsistent results.

Our objective was to compare the efficacy of posterior IAS myectomy with intrasphincteric Botox injection for treatment of IAS achalasia based on a meta-analysis of the literature.

Materials and methods

Information sources and literature search

A systematic literature search was performed to identify articles reporting cases of IAS achalasia. Common electronic databases as MEDLINE® (1950–present), EMBASE® (1966−present), ISI Web of Science℠ (1899–present) and the Cochrane Library (1898–present) were searched in April 2012 by using a combination of the following terms: "internal anal sphincter achalasia", "myectomy" AND "botulinum toxin injection". Reference lists of identified articles were screened for additional studies. There were no language or publication date restrictions. Duplicated articles were deleted.

Selection criteria and data extraction

Identified articles were reviewed by title, key words and abstract by one of the authors (F.F.). Only articles where IAS achalasia was diagnosed by RSB and ARM were included. All articles that did not contain original research data (e.g. letters, editorials, commentaries and reviews) and articles not giving adequate information regarding outcome were excluded. Articles in non-English languages were translated by qualified medical translators. An unblinded, standardized full-text assessment of relevant articles was independently performed by both authors (F.F. and P.P.). The data were extracted into an electronic datasheet in a standardized manner.

Data extracted from each article included study characteristics (authors, publication year, sample size, treatment method, follow-up time) and patient characteristics (age, symptoms, previous conservative or surgical therapies). The primary outcome of this analysis was whether or not bowel function required continued use of laxatives/rectal therapies after treatment of IAS achalasia. Secondary outcomes of intervention included specific (transient faecal incontinence, soiling, constipation) and overall complication rates. Furthermore, rate of non-response, need for subsequent surgical procedures and short- and long-term improvements were recorded.

Statistical analysis

Since not all complications and outcome parameters were reported in all articles, each specific complication and outcome parameter was recorded as the number of patients in which that item was present divided by the total number of patients in the cohorts that presented data on that item. This enabled the calculation of incidences for each specific complication and outcome. With these data, a cumulative meta-analysis was performed. Odds ratios (OR) with 95 % confidence interval (CI) were calculated. Statistical differences were considered as significant for a p value <0.05 (two tailed).

Results

Literature search result

The systematic literature search resulted in a total of 173 articles, of which 166 were identified by electronic

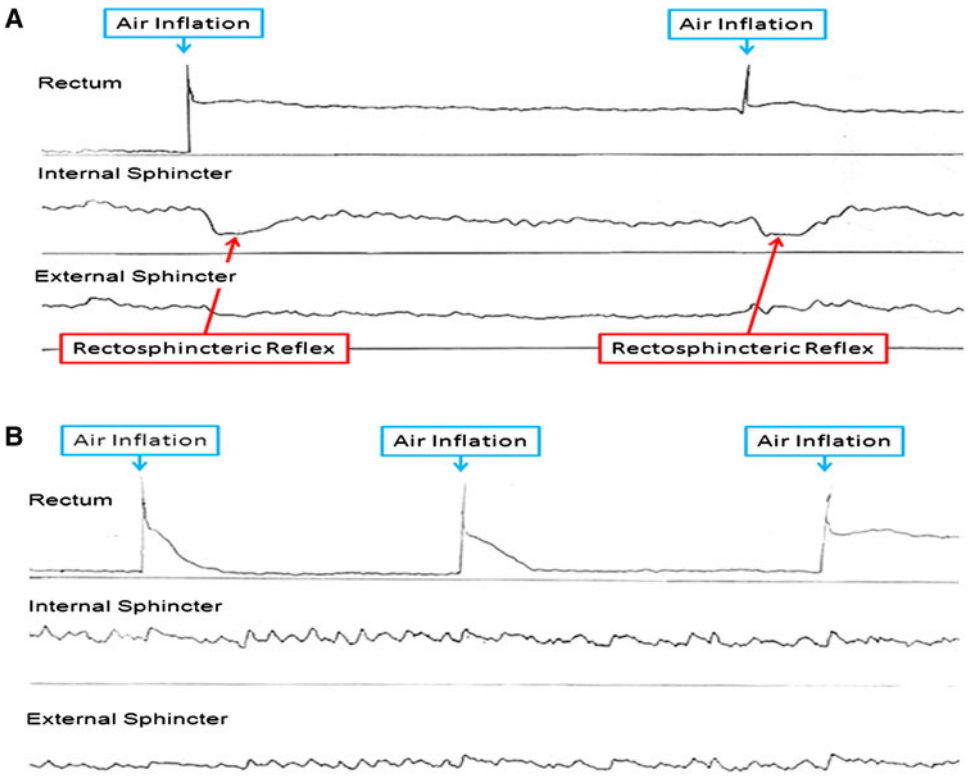

Fig. 1 Anorectal manometry showing **a** evidence of the rectosphincteric reflex on rectal balloon inflation in a normal IAS. **b** Absence of the rectosphincteric reflex on rectal balloon inflation and the presence of marked rhythmic activity of the IAS in a patient with IAS achalasia

database search and 7 by cross-referencing (Fig. 2). After removal of 83 duplicates, 90 titles, key words and abstracts were reviewed. Of these, 72 articles were excluded because after screening it emerged that these studies clearly did not meet the inclusion criteria as described. Eighteen articles met our criteria for inclusion and the full text was examined more in detail. Of these, two articles were excluded because they referred to results of already selected cohorts. In total, data from 16 studies (14 retrospective, 2 prospective), published from 1973 to 2009, were included in the quantitative synthesis. No randomized trials were identified.

Characteristics of included studies

The overall number of study subjects with IAS achalasia was 395, ranging from 4 to 73 patients per study. Study and patient characteristics are presented in Table 1. Posterior IAS myectomy (229/395; [58.0 %]) was more common than intrasphincteric Botox injection (166/395; [42.0 %]). Data on age at treatment were reported in 14 studies with a mean of 5.3 years (range 3.0–8.9). All included studies presented data on symptoms before treatment. The leading symptom was severe constipation (394/395; [99.7 %]), followed by soiling (31/67; [46.3 %]) and enterocolitis (2/65; [3.1 %]). Eight studies contained data on duration of symptoms with a mean of 2.9 years (range 0.8–4.1). Data on use of laxatives or rectal enemas (86/118; [72.9 %]) before the treatment and previous surgical therapies (33/95; [34.7 %]) were reported in seven studies. All included studies comprised data on follow-up time with a mean of 2.1 years (range 0.5–10.0).

Data on complications and outcomes

Data on the incidences for each specific complication and outcome parameters after treatment for IAS achalasia are presented in Table 2.

A cumulative meta-analysis revealed that regular bowel movements were significantly more frequent after posterior IAS myectomy (OR 0.53, [95 % CI 0.29–0.99]; $p = 0.04$). There was no significant difference in the continued use of laxatives or rectal enemas (OR 0.92, [95 % CI 0.34–2.53], $p = 0.89$) and in overall complication rates between both procedures (OR 0.68, [95 % CI 0.38–1.21]; $p = 0.19$). Looking at specific complications, the rate of transient faecal incontinence was significantly higher after intrasphincteric Botox injection (OR 0.07, [95 % CI 0.01–0.54]; $p < 0.01$). Constipation and soiling after treatment for IAS achalasia were not significantly different between both procedures (OR 0.66, [95 % CI 0.30–1.48]; $p = 0.31$ and OR 0.24, [95 % CI 0.03–2.07]; $p = 0.25$). The rate of non-response was significantly higher after intrasphincteric Botox injection (OR 0.52, [95 % CI 0.27–0.99]; $p = 0.04$). Subsequent surgical treatment was significantly more frequent after intrasphincteric Botox injection (OR 0.18,

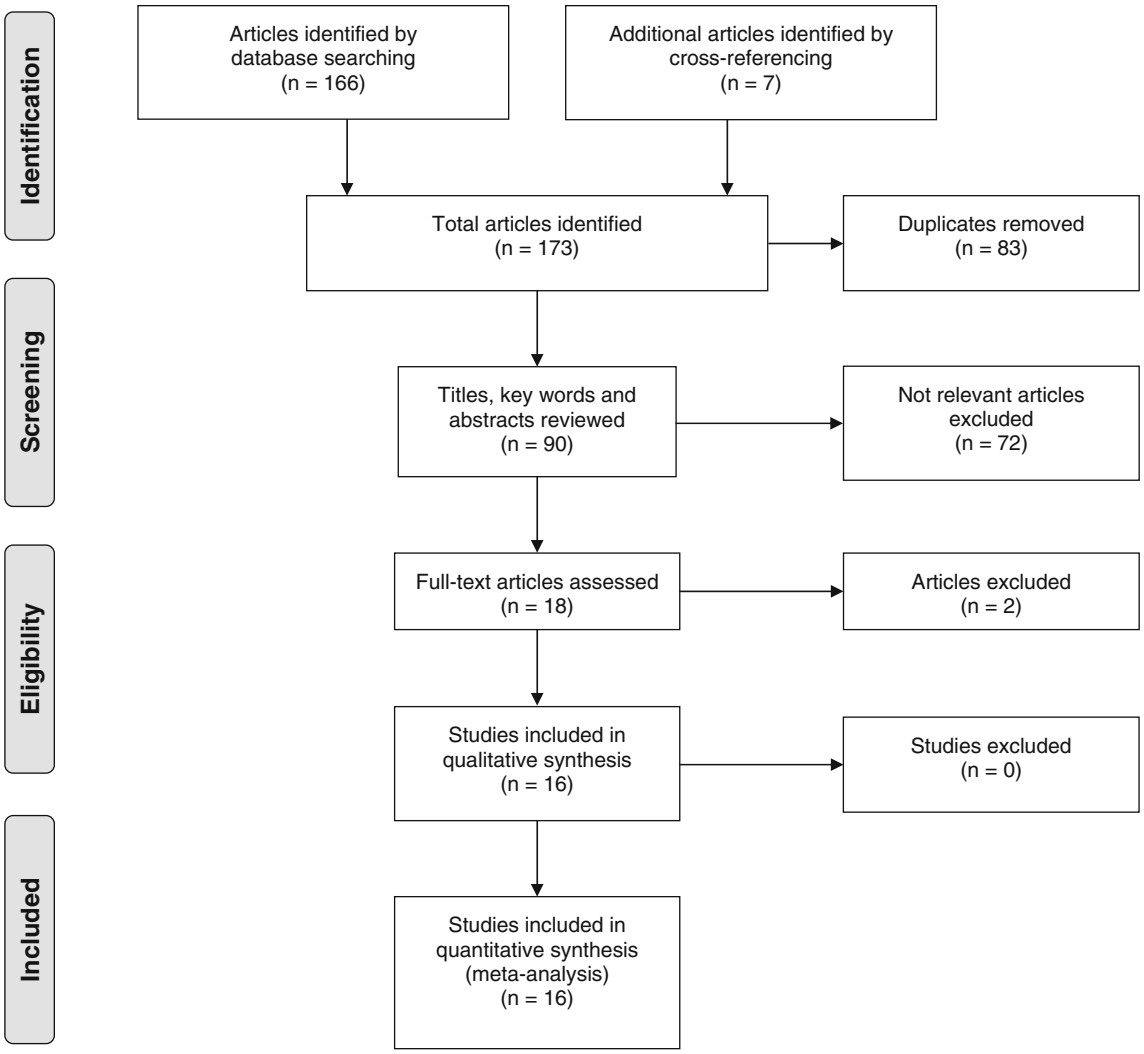

Fig. 2 Information flow through the different phases of the systematic review

[95 % CI 0.07–0.44]; $p < 0.0001$). Short- and long-term improvements were significantly more frequent after posterior IAS myectomy (OR 0.56, [95 % CI 0.32–0.97]; $p = 0.04$ and OR 0.25, [95 % CI 0.15–0.41]; $p < 0.0001$).

Data on classification of outcome after treatment for IAS achalasia were reported in all included studies (Table 3). A cumulative meta-analysis could not be performed as studies used different techniques for assessing outcome.

Discussion

Children with IAS achalasia usually present with severe constipation with or without soiling. However, the exact incidence of IAS achalasia is unknown. In 2002, De Caluwé et al. [14] reported an incidence of 4.5 % among 332 patients who were investigated for severe chronic constipation.

In the last 50 years, posterior IAS myectomy has been the treatment of choice for patients with IAS achalasia. In 1997, Langer and Birnbaum [20] presented their preliminary experience with intrasphincteric Botox injection for persistent constipation caused by IAS achalasia. Since then, promising short-term results have been reported following this less invasive procedure [21, 22]. As the studies that have been published of patients with IAS achalasia report inconsistent results and often comprise relatively small sample sizes, we performed a meta-analysis to find important outcome differences between these two procedures.

Our meta-analysis revealed that regular bowel movements were significantly more frequent after posterior IAS myectomy. Hecker et al. [23] reported that after posterior IAS myectomy, more than 90 % of their 32 patients had spontaneous defecation on a daily basis. De Caluwé et al. [14] and Doodnath et al. [15] reported similar results in their cohorts of patients after posterior IAS myectomy.

Table 1 Study and patient characteristics of included studies

Articles (references)	No. of subjects	Treatment method	Age at treatment in years (range)	Symptoms				Previous therapy		Follow-up time in years (range)
				Constipation	Soiling	Enterocolitis	Duration in years (range)	Conservative	Surgical	
Doodnath and Puri [15]	24	IAS myectomy	6.2 (2.0–12.0)	24	NR	NR	NR (NR)	NR	0	NR (4.0–14.0)
Koivusalo et al. [18]	8	Botox injection	8.1 (1.6–11.0)	7	5	1	NR (0.3–4.0)	7	3	1.6 (0.3–3.6)
Chumpitazi et al. [17]	43	Botox injection	5.3 (0.5–18.8)	43	NR	0	NR (NR)	12	NR	2.2 (NR)
Jiang et al. [19]	23	Botox injection	4.0 (3.0–11.0)	23	NR	NR	1.2 (0.2–2.2)	NR	23	1.0 (NR)
Foroutan et al. [27][a]	8	Botox injection	4.0 (3.0–8.0)	8	NR	NR	>0.5 (NR)	NR	NR	1.0 (NR)
Foroutan et al. [27][a]	11	IAS myectomy	3.0 (2.0–6.0)	11	NR	NR	NR (NR)	NR	NR	1.0 (NR)
Irani et al. [21]	24	Botox injection	8.9 (2.0–17.0)	24	17	NR	NR (NR)	NR	NR	0.5 (NR)
Heikkinen et al. [16]	10	IAS myectomy	4.5 (1.0–10.0)	10	NR	0	NR (NR)	10	NR	10.0 (7.0–16.0)
Rodriguez and Flores [28]	14	Botox injection	NR (NR)	14	NR	NR	NR (NR)	NR	2	NR (2.0–6.0)
Ciamarra et al. [29]	20	Botox injection	5.8 (1.6–10.0)	20	7	NR	NR (NR)	20	NR	0.6 (0.1–1.5)
Messineo et al. [22]	4	Botox injection	3.3 (0.3–12.0)	4	NR	NR	0.8 (0.3–2.0)	NR	1	1.0 (0.3–1.4)
De Caluwé et al. [14]	15	IAS myectomy	6.2 (2.0–12.0)	15	2	NR	3.9 (0.5–12.0)	15	NR	3.7 (2.0–6.0)
Minkes and Langer [26]	18	Botox injection	4.0 (1.0–13.0)	18	NR	NR	4.0 (1.0–12.0)	18	2	0.5 (NR)
Langer and Birnbaum [20]	4	Botox injection	5.1 (4.0–8.0)	4	NR	1	3.2 (1.8–6.6)	4	2	0.8 (0.6−0.8)
Krebs and Acuña [24]	64	IAS myectomy	NR (0.1–14.0)	64	NR	NR	NR (N)R	NR	NR	NR (0.1–9.0)
Holschneider et al. [25]	73	IAS myectomy	NR (NR)	73	NR	NR	NR (NR)	NR	NR	NR (0.1–3.0)
Hecker et al. [23]	32	IAS myectomy	6.0 (0.1–14.0)	32	NR	NR	4.1 (0.5–14.0)	NR	NR	NR (0.5–3.0)

NR not reported

[a] Authors reported retrospectively on both treatment methods

Table 2 Data on complications and outcome after treatment for IAS achalasia of included studies

Complications and outcome	Posterior IAS myectomy	Intrasphincteric Botox injection
Regular bowel movements	188/218 (86.2)	70/91 (76.9)
Continued use of laxatives/ rectal enemas	38/156 (24.4)	20/83 (24.1)
Overall complication rate	31/229 (13.5)	27/144 (18.8)
Intermediate faecal incontinence	0/112 (0.0)	15/132 (11.4)
Constipation	21/145 (14.5)	11/53 (20.4)
Soiling	7/49 (14.3)	1/26 (3.8)
Non-response rate	18/208 (8.7)	25/162 (15.4)
Need for subsequent surgical treatment	7/154 (4.5)	19/99 (19.2)
Short-term improvement (<6 months)	20/229 (87.8)	133/166 (80.1)
Long-term improvement (>6 months)	195/229 (85.2)	84/143 (58.7)

Data are presented as *n*/*N* (%)

IAS internal anal sphincter

Table 3 Data on classification of outcome after treatment for IAS achalasia of included studies

Classification of outcome[a]	Posterior IAS myectomy	Intrasphincteric Botox injection
Excellent	58/218 (26.6)	24/166 (14.5)
Good	129/229 (56.3)	73/166 (44.0)
Fair/moderate	14/218 (6.4)	32/166 (19.3)
Poor	14/218 (6.4)	35/166 (21.1)

Data are presented as *n*/*N* (%)

IAS internal anal sphincter

[a] Follow-up data were not reported for all patients

Furthermore, short- and long-term improvements in constipations were significantly more frequent after posterior IAS myectomy compared to intrasphincteric Botox injection. Several authors reported very satisfactory results in their patients with IAS achalasia following posterior IAS myectomy [15, 16, 24, 25]. Although there were no significant differences in overall complication rates, the rate of transient faecal incontinence was significantly higher after intrasphincteric Botox injection than after posterior IAS myectomy. Irani et al. [21] detected faecal soiling after Botox treatment in 5 of 24 (20.8 %) patients with IAS achalasia, lasting <1 week in 4 patients and 4 weeks in 1 patient. A number of other authors reported the same experience after Botox injection [17, 26]. Furthermore, the rate of non-response was significantly higher after intrasphincteric Botox injection. Koivusalo et al. [18] observed no improvements in 37.5 % of patients with IAS achalasia after Botox injection treatment. Chumpitazi et al. [17] found that short-term improvement after initial Botox injection predicted favourable long-term reponse and repeated injections after initial failure were of no benefit in these patients. In addition, the relapse rate after the use of intrasphincteric Botox is quite high [22, 26–28]. Ciamarra et al. [29] reported that 4 of 20 (20.0 %) patients with IAS achalasia, who initially responded to the treatment with Botox, relapsed and underwent IAS myectomy.

In conclusion, the rate of transient faecal incontinence, non-response and subsequent surgical treatment was significantly higher after intrasphincteric Botox injection compared to posterior IAS myectomy. This meta-analysis indicates that the majority of patients with IAS achalasia can be treated successfully by posterior IAS myectomy with a significantly higher rate of long-term improvements. Therefore, posterior IAS myectomy appears to be a more effective treatment option compared to intrasphincteric Botox injection in patients with IAS achalasia.

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