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[Intervention Review]

Nitrates for achalasia

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ABSTRACT

Background

Achalasia is a disease that impairs oesophageal motility. Although nitrates have been used to treat achalasia for a long time, the effectiveness of nitrates for achalasia is still controversial. Newer therapies have to some extent superceded the use of nitrates for achalasia, but nitrates may still be used in early or mild disease, in patients who are unsuitable for surgery or invasive procedures, or when botulinum injection therapy has failed.

Objectives

To quantify short-term and long-term effects of nitrate therapy in participants with achalasia.

Search methods

Trials were identified by searching the Cochrane Controlled Trials Register (Issue 4-2001), MEDLINE (1966-2001), EMBASE (1980-2001), LILACS - Latin American and Caribbean health science literature (1982-2001) and CBM-Chinese Biomedical database(1980-2000). Additionally, all references in the identified trials were checked for further relevant trials. An updated search was run on the Cochrane Library, MEDLINE, and EMBASE in September 2003, October 2004, September 2005 and December 2008.

Selection criteria

All randomised controlled trials involving achalasic participants given any type of nitrates were included.

Data collection and analysis

Data were extracted by two independent observers.

Main results

Two randomised cross-over studies were found, but no results were included. Due to the design of the studies and the method of reporting the results in the original paper it was not possible to extract the necessary information to examine any of the outcomes.

Authors' conclusions

From most of the single reports we found, after intake of nitrates (either nitroglycerin or isosorbide dinitrate), there was a fall in lower oesophageal pressure and improvement of radionuclide esophageal emptying compared to the baseline. From the available evidence, we cannot provide any implications for practice. Appropriately designed, parallel group, randomised controlled trials with long term follow-up are needed to determine the effects of nitrates for achalasia.

PLAIN LANGUAGE SUMMARY

Nitrates (medicines) for achalasia (impaired swallowing)

Achalasia is a condition where the lower part of the oesophagus leading to the stomach is unable to relax normally after swallowing. Food may become stuck there rather than going through into the stomach. Although the cause of achalasia is not known, it is well demonstrated that loss of oesophageal neurons is the underlying problem. Patients may experience dysphagia, regurgitation of food, retrosternal pain and so on. Nitrates are drugs that may relax the muscle and they are used to try to relieve the symptoms. They can be taken either as tablets, or absorbed under the tongue. Nitrates can be used in patients with mild symptoms, where it is not necessary to perform an invasive procedure such as surgery or if the patient is not a suitable candidate for surgery for some other reason. Nitrates can also be used if there is no response to injections of botulinum toxin to relax the muscle of the oesophagus. One other widely used option for the treatment of achalasia is dilation of the oesophagus using endoscopic methods. This review found there is not enough evidence from trials to show if nitrates are an effective treatment to relieve achalasia.

BACKGROUND

Description of the condition

Achalasia is a disease that impairs oesophageal motility. This condition occurs when the lower oesophageal sphincter (LOS) fails to relax normally on swallowing. This results in food being retained above the constricted part of the oesophagus. The epidemiology of achalasia has not been extensively studied. The annual incidence has been estimated at 0.5 to 1.2 per 100,000 in Great Britain, Ireland, and the United States (Mayberry 1987; Mayberry 1985; Earlam 1969; Howard 1992). It is seen in all races and in both sexes. The cause of this disease is unknown. Lower oesophageal sphincter relaxation is abnormal because the inhibitory nerves to the sphincter are either absent or functionally impaired. Symptoms of achalasia include dysphagia, regurgitation of food and retrosternal pain, which is increased when taking food. Oesophageal manometry, radiology (and, to a lesser extent, endoscopy) may help to establish a diagnosis and exclude other causes of esophageal obstruction. The oesophageal body usually is dilated and terminates in a narrowed segment. The classic manometric findings of achalasia are high resting pressure of LOS and low amplitude simultaneous contractions of the oesophageal body on deglutition.

Description of the intervention

All forms of interventions for achalasia are directed at relieving the obstruction, rather than providing a cure for the underlying causes of the disease. Pneumatic dilation of the lower esophageal sphincter under endoscopy is considered the definitive treatment for achalasia. Surgical myotomy, including the recently more preferred laparoscopic approach, provides the most effective and sustained clinical response, but given the related risks and complications of surgery, it is usually reserved for those for whom pneumatic balloon dilatations fails. Alternative medical interventions have certain advantages above those invasive methods, but their effect is controversial; usually offering only a mild, transient improvement. Such medical interventions include nitrates, calcium channel blockers and, recently, botulinum toxin. Nitrates and calcium channel blockers taken immediately before meals may somewhat relieve dysphagia. However, the long-term efficacy of these interventions is not known.

How the intervention might work

Early in 1940s, there were reports of the use of nitroglycerin in achalasia (Ritvo 1940; Field 1944). Since the mid-1970s, nitrates have been used widely as a vasodilator for cardiovascular diseases. Nitroglycerin and other nitrate-containing compounds activate guanylate cyclase, increasing the synthesis of cyclic GMP (guanosine 3', 5' monophosphate) in gastrointestinal smooth muscle (Katsuki 1977). The protein kinase produced by the interaction of guanylate cyclase with nitric acid alters the phosphorylation process in smooth muscle, resulting in dephosphorylation of the light chain of myosin and inhibition of the normal contractile process of smooth muscle. On the other hand, nitrate liberates nitric oxide (NO), which is an inhibitory non-adrenergic non-cholinergic (NANC) neurotransmitter mediated by cyclic GMP. Blocking the generation of NO was shown to inhibit the relaxation of the lower esophageal sphincter of animals (opossum, dog) and humans *in vitro* (Tottrup 1991). There are some reports that nitroglycerin provides symptomatic improvement for patients with oesophageal motility disorders by relaxing smooth muscle.

Why it is important to do this review

The effects of medical drugs are relatively mild in achalasia. Among the great variety of compounds have been tried, nitrates are probably the most effective drugs. However, most trials to date were not controlled and usually included a small number of patients.

Due to the relatively short half-life of nitrates, it is difficult to determine their long-term efficacy. However, if such medical interventions do provide benefits in the management of achalasia and delay the process of the disease, then they may be more acceptable to patients than the current endoscopic approaches.

Nitrates are usually dispensed in sublingual and tablet formulations. Sublingual therapy yields maximum plasma concentration in several minutes, but has a rapid fall-off. Sublingual therapy is advised for patients with achalasia because of the possibility of prolonged oesophageal transit and the resultant delayed gastric absorption. However, many patients prefer to take medication orally rather than sublingually.

OBJECTIVES

To quantify short-term and long-term effects of nitrate treatment in participants with achalasia. Nitrates compared with any other types of intervention will be considered, this includes medical therapies, such as calcium-channel blockers, anticholinergic agents, beta-adrenergic agonists and botulinum toxin, endoscopic therapies, surgical therapies, placebo and no intervention.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials with or without blinding. It was not necessary for the control group to receive a placebo.

Types of participants

Participants with achalasia as diagnosed by symptoms and radiology or manometric findings of the oesophagus are included. Cardiac carcinoma and achalasia of Chagas' disease were excluded.

Types of interventions

The drug therapies reviewed are:

- isosorbide dinitrate
- nitroglycerin (glyceryl trinitrate)
- pentaerythrital
- amyl nitrite
- octyl nitrite

All taken orally or sublingually or transdermally.

Types of outcome measures

Primary outcomes

1. Occurrence of invasive procedure (that is, whether a participant still required treatment by invasive procedures including dilatation and surgery).

Secondary outcomes

1. Improvement of symptoms (e.g. dysphagia, regurgitation of food, retrosternal pain).
2. Reduction of LOS pressure.
3. Oesophageal emptying rate.
4. Side effects: headache, flush, change of blood pressure.

Search methods for identification of studies

Electronic searches

Trials were identified by searching the Cochrane Controlled Trials Register (Issue 4-2001), MEDLINE (1966-2001), EMBASE (1980-2001), LILACS - Latin American and Caribbean health science literature (1982-2001) and CBM-Chinese Biomedical database(1980-2000). Additionally, all references in the identified trials were checked for further relevant trials. An updated search was run on the Cochrane Library, MEDLINE, and EMBASE in September 2003, October 2004, September 2005 and December 2008.

The Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE, Sensitivity maximising version, Ovid format (Higgins 2008), was combined with the search terms in Appendix 1 to identify randomised controlled trials in MEDLINE. The MEDLINE search strategy was adapted for use in the other databases searched.

Searching other resources

Reference lists from trials selected by electronic searching were handsearched to identify further relevant trials.

Data collection and analysis

Selection of studies

Titles and abstracts identified for possible inclusion in the review were checked by two reviewers. The full text of all studies of possible relevance was obtained for independent assessment by both reviewers. The reviewers decided which trials fit the inclusion criteria, and graded the methodological quality of the studies. Any disagreement was resolved by discussion between the reviewers and consultation with the third reviewer.

Data extraction and management

Data extraction was performed by a single reviewer and checked by a second reviewer.

Assessment of risk of bias in included studies

Methodological quality of included studies

The methodological quality of the included trials was assessed with particular emphasis on the allocation concealment, which was ranked using the Cochrane approach:
Grade A: Adequate concealment,
Grade B: Uncertain,
Grade C: Clearly inadequate concealment.

The methodological quality of studies was also be documented using the following criteria:

- baseline comparison of experimental groups,
- explicit diagnostic criteria,
- completeness of follow-up,
- blind outcome assessment and
- blind administration of nitrates.

Measures of treatment effect

Data were extracted based on the intention to treat principle. Odds ratios for incidence of invasive procedure, improvement of symptoms, LOS pressure decrease, oesophageal emptying, and side effects were calculated. Numbers needed to treat (NNT) for avoiding invasive procedure, improvement of symptoms, oesophageal emptying, and numbers needed to harm (NNH) of side effects were also determined. 95% confidence intervals (CI) were calculated for all outcomes.

Data synthesis

No meta-analysis was possible. We had intended to use the following methods to pool data. For dichotomous outcomes, such as incidence of invasive procedure, improvement of symptoms, the fixed-effect Mantel-Haenszel odds ratio would have been used. For continuous outcomes, such as LOS pressure decrease, oesophageal emptying, the fixed-effect mean difference would have been used.

RESULTS

Description of studies

Results of the search

Twenty-seven references were considered during eligibility assessments as potential randomised controlled trials which fit the inclusion criteria, and were reviewed.

Included studies

Two trials were identified that satisfied the inclusion criteria (see Characteristics of included studies).

In both studies participants received all interventions in a random order (Gelfond 1982; Wong 1987). In one study (Gelfond 1982), fifteen participants received isosorbide dinitrate (5mg) and nifedipine (20mg). Each participant received each intervention for "at least one week", it was unclear how long each participant received each intervention for or what order the interventions were received in. In the other study (Wong 1987), fifteen participants received nitroglycerin (0.4mg s.l), normal saline (0.25ml s.c.), terbutaline sulfate (0.25 mg s.c.) and aminophylline (5.0 mg kg-1). Each participant received one dose of each intervention on four separate days, it was unclear what the time span was in between each intervention. The order in which participants received interventions in was not given in the paper.

Neither study had an appropriate design for measuring the invasive procedure rate or long term effects. In Gelfond 1982, the symptom relief was assessed subjectively by the physician. LOS pressure was reported at five minute intervals after initial intervention, oesophageal emptying and side effects were measured at the end of each intervention phase. It was unclear how often readings of oesophageal emptying were taken, but measurements were started ten minutes after isosorbide dinitrate administration and 30 minutes after nifedipine administration. In Wong 1987, LOS pressure was measured after intervention but after different timings for each intervention (10, 20, 30, 45 and 60 minutes after terbutaline sulfate and saline; five, 10, 20 and 30 min

after nitroglycerin; and immediately, 10, 20, 30, 45 minutes after aminophylline) and esophogeal emptying rate was only measured for participants that responded to the intervention.

Excluded studies

Twenty-five studies were excluded (see Characteristics of excluded studies), 21 (77.8%) were studies that did not compare nitrates and four (14.8%) were non-randomised comparisons of nitrates. Of the non-randomised studies, two were before and after studies (Gelfond 1981; Wang 1988), one a non-randomised study comparing nifedipine (nine participants) to isosorbide dinitrate (seven participants) (Bortolotti 1994), and one compared amyl nitrate with glyceryl trinitrate (seven participants) and with Mercury bougie (five participants) (Douthwaite 1943).

Risk of bias in included studies

Please see the risk of bias tables in the 'Characteristics of included studies' table.

Neither of the two included studies (Gelfond 1982; Wong 1987) mentioned method of randomisation or allocation concealment, nor was it clear whether the participants were blind to their allocation, but both studies mentioned that the assessor of LOS was blind.
Both studies had explicit diagnostic criteria; Gelfond 1982 reported the number of marked dilated oesophagus in the group, indicate the severity of the group. This study also had a follow-up of 8-14 months, but this is not relevant for a study with repeated interventions. Both studies took baseline assessments, but comparability between groups was not relevant because of the differences in the design of the studies.

Effects of interventions

It was not possible to distinguish the randomised groups in either study, the results presented per intervention were for all participants regardless of the order the interventions were received in. Meta analysis was not possible. The trial investigators were contacted to obtain this information. Unfortunately, Professor Gelfond died several years ago. His colleague, who worked with him on the same research study, could not provide further materials of the results of this, which was published in 1982. To date we have received no response from the authors of Wong 1987.

It was not possible to present the results from each study separately. The analyses that the studies presented for LOS pressure were comparisons of each intervention to baseline, no comparison between interventions was done and no within participant information was available. In Gelfond 1982, although data on oesophageal emptying, symptom relief and side effects were given for each participant, making it possible to make a comparison between interventions, we have not made this comparison because there was no pre-defined duration for a phase, and it was not clear what determined the duration of intervention for each participant.

DISCUSSION

Only two randomised studies were found which compared nitrate to alternate intervention for achalasia. The designs and reporting methods of these were not appropriate for meta analysis. In both studies, participants received all interventions in a random order. The primary outcome (occurrence of invasive procedure) cannot be considered when participants receive all interventions. One study (Wong 1987) looked only at the short-term outcomes. The other study (Gelfond 1982) did look at longer term effects, but it was unclear what the duration of intervention was or what determined this. Appropriately designed parallel group randomised controlled trials with long term follow up are needed to confirm the effect of nitrates for achalasia.

Since this review was first written, newer therapies have to some extent superceded the use of nitrates and other oral medications (calcium channel blockers) as treatments for achalasia (Vaezi 1998). Nitrates can still be used in patients with mild symptoms, in cases where the patient is not a suitable candidate for surgery for, or when treatment of mild disease does not warrant the use of an invasive procedure. Nitrates can also be used if there is no response to injections of botulinum toxin to relax the oesophagus. One other widely used option for the treatment of achalasia is endoscopic pneumatic dilation of the oesophagus. This review found there is not enough evidence from trials to show if nitrates are an effective treatment to relieve achalasia.

AUTHORS' CONCLUSIONS

Implications for practice

We found no suitable randomised controlled trials and therefore cannot make any recommendations for practice. Although non-randomised trials have found evidence that nitrates relieve symptoms of achalasia and promote some measurements (Gelfond 1981; Wang 1988; Bortolotti 1994; Douthwaite 1943), evidence of side effects such as flush, headache and blood pressure change have also been reported (Douthwaite 1943; Gelfond 1981; Gelfond 1982; Rozen 1982a; Bassotti 1988). We therefore suggest that nitrates should only be used as an intervention in randomised trials, until further evidence has been found.

Implications for research

There are no placebo-controlled randomised trials and only two randomised cross-over controlled trials. More randomised controlled trial data would be needed to determine the effects of nitrates. Many clinical trials we investigated only reported the acute effect of nitrate, that is the effects seen within an hour. Data on patient outcomes when nitrates are used for symptom relief are still lacking. The results of one retrospective study indicated that elderly patients with achalasia responded more poorly to nitrate than the younger patients; prospective studies are needed to confirm this (Ghosh 1994). The long term effects of nitrates, when given continuously, should be investigated, such as recording patients' responses at one month or one year.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gelfond 1982

Methods	Randomised blind cross over controlled trial.
Participants	6 men, 9 women, mean age 44 yrs.
Interventions	Isosorbide dinitrate 5mg v. nifedipine 20mg sublingually.
Outcomes	LOS pressure; radiolabelled test meal of oesophageal retention.

Gelfond 1982 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "each received at random either ID or Nif sublingually".
Allocation concealment?	High risk	Quote: "Because of the different routes of drug administration, the participants were not blinded as to whether they received ID or Nif".
Blinding? clinical response	Low risk	Quote: "the clinical response was assessed by the physician without knowing or asking which medication was given".
Blinding? Manometric examinations	Low risk	Quote:"Analysis of the manometric examinations was made without knowing which drug was administered.".
Incomplete outcome data addressed? All outcomes	Low risk	No incomplete outcome data.
Free of selective reporting?	Low risk	Yes
Free of other bias?	Low risk	Yes

Wong 1987

Methods	Randomised blind cross over controlled trial.
Participants	11 men, 4 women. Mean age 28 years.
Interventions	Nitroglycerin 0.4 mg s.l. and normal saline 0.25ml s.c.
Outcomes	LOS pressure; radiolabelled test meal of oesophageal retention.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: On four separate days, participants received one of four medications "in a random order".
Allocation concealment?	High risk	The four medications were given by different way, either s.l., s.c., or i.v.
Blinding? clinical response	Unclear risk	Did not report clinical response for every participant.
Blinding? Manometric examinations	Low risk	Quote: "After studying 15 participants, recordings of individual station pull-throughs were removed from the entire tracing, coded, randomised, and read by a single un-informed observer."

Wong 1987 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Yes
Free of selective reporting?	Unclear risk	Did not report clinical response for every participant.
Free of other bias?	Low risk	Yes

i.v. intravenous
s.l. sub lingual
s.c. sub cutaneous

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Achkar 1995	Review
Allescher 1993	Review
Bassotti 1988	No control
Bassotti 1999	Review
Bortolotti 1994	Non-randomized controlled trial
Bourgeois 1992	No intervention with nitrates
Douthwaite 1943	Non-randomised controlled trial
Efrati 1996	Case-report
Ferguson 1981	Performed on participants with chest pain
Furuya 1995	Case-report
Gelfond 1981	No control
Ghosh 1994	No control
Hildebrand 1993	Review
Kikendall 1980	Study performed on healthy volunteers
Krivchenya 1990	No control medication
Ona 1980	Case report
Reynolds 1989	Review
Rozen 1982a	No control
Rozen 1982b	No control

Study	Reason for exclusion
Schroeder 1985	Review
Stanley 1955	A group of participants with cardiospasm were given urecholine, dibuline, and finally nitroglycerin. The author did not provide the exact time interval between each medicine and did not provide exactly how long after nitroglycerin intake participants were measured for oesophageal emptying.
Storr 1999	Review
Swamy 1977	Performed on participants with esophageal spasm, no control medication.
Tack 1991	Review
Traube 1985	Review
Vaezi 1998	Review
Wang 1988	No control medication

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp nitrates/
2. nitrat$.tw.
3. exp isosorbide dinitrate/
4. (isosorbide adj3 dinitrate).tw.
5. pentaerythrit$.tw.
6. exp nitroglycerin/
7. nitrogly$.tw.
8. (glyceryl adj3 trinitrate).tw.
9. exp amyl nitrite/
10. (amyl adj3 nitr?te).tw.
11. or/1-10
12. exp esophageal achalasia/
13. achal$.tw.
14. cardiospasm$.tw.
15. (spas$ adj5 cardia).tw.
16. (megaesophagus or megaoesophagus).tw.
17. or/12-16
18. 11 and 17
19. limit 18 to yr="2005 - 2008"

WHAT'S NEW

Date	Event	Description
21 September 2010	Amended	Contact details updated.
3 February 2010	Review declared as stable	Searches, tables and figures last updated February 2010. Declared stable and no future updates planned.

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 4, 2002

Date	Event	Description
3 February 2010	New search has been performed	Updated
30 October 2008	Amended	Converted to new review format
13 September 2005	New search has been performed	New studies sought but none found
21 August 2002	Amended	Minor update

CONTRIBUTIONS OF AUTHORS

All authors contributed to development of the protocol, writing the review and subsequent updates.

ZW composed the protocol and the review. GE described the included and excluded studies and contributed to communications with trial investigators. YW supervised the work.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane Centre, Chinese Centre of Evidence-based Medicine, West China Hospital of Sichuan University, China.

External sources

- China Medical Board of New York (Grant number: 98-680), China.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

At the update in 2010, we added change in blood pressure (a side effect) to the list of outcomes.

NOTES

Searches, tables and figures last updated February 2010. Declared stable and no future updates planned.

INDEX TERMS

Medical Subject Headings (MeSH)

Esophageal Achalasia [*drug therapy]; Nitric Oxide Donors [*therapeutic use]; Nitro Compounds [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans