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Botulinum toxin type A versus anticholinergics for cervical dystonia (Review)

Costa J, Espírito-Santo CC, Borges AA, Moore P, Ferreira J, Coelho MM, Sampaio C

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[Intervention Review]

Botulinum toxin type A versus anticholinergics for cervical dystonia

João Costa[1], Cláudia C Espírito-Santo[1], Ana A Borges[1], Peter Moore[2], Joaquim Ferreira[1], Miguel M Coelho[1], Cristina Sampaio[1]

[1]Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina de Lisboa, Lisboa, Portugal. [2]The Walton Centre for Neurology and Neurosurgery, NHS Trust, Liverpool, UK

Contact address: João Costa, Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina de Lisboa, Av. Prof. Egas Moniz, Lisboa, 1649-028, Portugal. joaoncosta@sapo.pt.

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ABSTRACT

Background

Cervical dystonia is the most common form of focal dystonia. It is characterized by involuntary posturing of the head and frequently is associated with neck pain. Disability and social withdrawal are common. Most cases are idiopathic and generally cervical dystonia is a life-long disorder. Botulinum toxin Type A (BtA) is now the first line therapy. Before BtA, anticholinergics were the most widely accepted treatment, so it is important to understand how these two treatments compare.

Objectives

To compare the clinical efficacy and safety of BtA versus anticholinergic drugs in the treatment of cervical dystonia.

Search methods

We searched the Cochrane Movement Disorders Group trials register (June 2003), the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2003), MEDLINE 1977 to June 2003), EMBASE (1977 to June 2003) and reference lists of articles. We also contacted manufacturers and researchers in the field.

Selection criteria

Randomised studies comparing BtA versus any anticholinergic drug for the treatment of cervical dystonia.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data. Study authors were contacted for additional information. Adverse effects information was collected from the trials.

Main results

We found only one trial suitable for inclusion and accordingly no meta-analysis was performed. It compared BtA versus trihexyphenidyl in 66 patients with cervical dystonia. Although this was a relatively small trial with short duration, the results can probably be generalized for the population, since the trial appears to be unbiased and produced clear clinically significant results. The results favoured BtA, and the difference was similar in size to that obtained in a systematic review comparing BtA with placebo. BtA was better tolerated.

Authors' conclusions

The available evidence suggests that BtA injections provide more objective and subjective benefit than trihexyphenidyl to patients with cervical dystonia. We could not draw any conclusions about other anticholinergic drugs. Future trials should explore the role of anticholinergic drugs in patients that do not get benefit with BtA.

PLAIN LANGUAGE SUMMARY

BtA injections provide more objective and subjective benefit than trihexyphenidyl to patients with cervical dystonia.

Cervical dystonia is characterized by involuntary posturing of the head and frequently is associated with neck pain. Disability and social withdrawal are common. Botulinum toxin Type A (BtA) is now the first line therapy but previously anticholinergics were the most widely accepted treatment. This review demonstrated that BtA injections are better than trihexyphenidyl, reduce involuntary muscular movements and tremor, reduce pain, and have fewer adverse effects as measured by objective scales and subjectively by patients.

BACKGROUND

Cervical dystonia, also called spasmodic torticollis, is a focal dystonia characterized by an involuntary posture of the head away from its normal central position (Foltz 1959). It may be dominated by sustained posture, by spasm, jerks or tremor, or there may be a combination of these features. 70% of patients have associated neck or shoulder pain (Chan 1991). Disability is common, with functional impairment and embarrassment causing social withdrawal. Many patients cannot work. Cervical dystonia is the most common form of focal dystonia with an estimate prevalence rate in Europe of 5.7/100000 (ESDE 2000), although rates of 8.9/100000 have been reported in the USA (Nutt 1988).

Most cases of cervical dystonia are idiopathic and about 12% have a family history (Jankovic 1991). Cervical dystonia can also be secondary to trauma or musculo-skeletal, spinal cord, intracranial, ocular and vestibular disorders. There are a few psychogenic cases. The pathophysiology of cervical dystonia probably relates to abnormal execution of motor programs. (Kanovsky 2003; Klier 2002).

The natural course of cervical dystonia remains unclear and spontaneous remissions have been reported with an estimated prevalence of 10% (Jahanshahi 1990). However, in the vast majority, cervical dystonia is a life-long disorder, and in a few cases may progress to segmental or generalized dystonia.

Cervical dystonia is classified according to the dominant head position or movement. Rotatory (simple) torticollis is the most common type (over 50%) (Chan 1991). Other common patterns are laterocollis, retrocollis and complex torticollis.

Many drugs have been administered to patients with cervical dystonia, with variable and questionable benefits. Anticholinergic drugs are the only group that have been consistently considered efficacious (Cullis 1989; Lang 1989) although only small and methodologically poor Randomised Controlled Trials (RCTs) are available.

Botulinum toxin (Bt) is a natural product synthesised by an anaerobic bacterium, Clostridium botulinum. It is responsible for the food poisoning disease botulism. Different strains of Clostridium botulinum produce seven immunologically distinct forms of botulinum neurotoxin labelled BtA to BtG. These potent neurotoxins are metalloproteases that block the release of acetylcholine at the neuromuscular junction though the cleavage of different peptide bonds that are crucial components in synaptic vesicle membrane fusion. The resulting impairment of neuromuscular transmission causes a flaccid paralysis (Brin 2002).

Clinical use of BtA began in the early 1980s, and several RCTs have suggested it is effective and safe in a variety of focal dystonias (Costa 2000). It has become the first line therapy for cervical dystonia in recent years. However, not all patients respond well to BtA, and 5 to 10% become resistant to it after a number of treatment cycles. This resistance is usually long lasting.

Since anticholinergics were the most widely accepted treatment before BtA became available, it is important to understand how these two treatments compare. To address this issue we systematically reviewed the randomised controlled clinical trials that compare BtA with anticholinergics in cervical dystonia.

OBJECTIVES

To compare the clinical efficacy and safety of Botulinum Toxin Type A (BtA) versus Anticholinergic drugs in the treatment of cervical dystonia.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised, controlled, double blind trials of BtA versus anticholinergics. Trials in which allocation was not adequately concealed were excluded.

Types of participants

Patients of any age with a clinical diagnosis of idiopathic cervical dystonia. We allowed previous therapy with BtA, whether patients were still responding to BtA (A-responders) or not (A-resistant), and we allowed concomitant medical therapies.

Types of interventions

Intramuscular injections of BtA versus anticholinergic drugs. We allowed all techniques (eg. EMG guided or not) and administration schedules of BtA administration.

Types of outcome measures

For each trial, we identified the number of patients originally allocated at random to each treatment group. For both groups, we sought outcome information for all the patients that had that outcome measured.
The primary outcomes were:
Improvement in symptomatic rating scales (any)
Secondary outcomes:
(1) Changes in subjective evaluation of clinical status both by patients and clinicians;
(2) Changes in pain scores;
(3) Adverse reactions (frequency and severity).

Search methods for identification of studies

We conducted searches from 1977, which was the first year that Bt was used therapeutically. We identified relevant trials from the following sources:
(1) Cochrane Movement Disorders Group Specialised Register (June 2003);
(2) Cochrane Central Register of Controlled Trials (CENTRAL) The Cochrane Library Issue 2, 2003);
(3) MEDLINE (1977 to June 2003);
(4) EMBASE (1977 to June 2003);
We screened titles, keywords and abstracts of the citations downloaded from the electronic searches, and obtained full copies of reports of potentially suitable trials for further assessment.
The search strategy also included:
(5) Reference lists of located trials and BtA review articles;
(6) Handsearch of Movement Disorders Journal and international congresses of movement disorders and botulinum toxins (1985 to June 2002);
(7) Personal communication with other researchers in the field;
(8) Contact with the drug manufacturers (Allergan and Ipsen).
(9) If necessary, we contacted authors of published trials for further information and unpublished data.
The search strategy for MEDLINE and Central/CCTR is given below. The search strategy was modified for EMBASE.
1.Botulinum toxins/
2.Botulinum Toxin Type A/
3.botulin$ and tox$.tw
4.dyspor$ or oculinu$ or boto$.tw
5.or/1-5
6.Cholinergic Antagonists/
7.anticholinerg*.tw
8.Benztropine/
9.Benztropine.tw
10.Biperiden/
11.Biperiden.tw
12.Dicyclomine/
13.Dicyclomine.tw
14.Orphenadrine/
15.Orphenadrine.tw
16.Procyclidine/
17.Procyclidine.tw
18.Scopolamine/
19.Scopolamine.tw
20.Trihexyphenidyl/
21.Trihexyphenidyl.tw
22.or/6-21
23.cervical dystonia/
24.torticollis/
25.cervic$ and dysto$.tw
26.torticol$.tw
27.or/23-26
28.5 and 22 and 27
29.limit 28 to human

Data collection and analysis

Three reviewers (Costa J, Borges A, Espírito-Santo C) independently assessed the studies identified by the search strategy, to iden-

tify potentially suitable trials for the review according to the criteria outlined above. We resolved disagreements about inclusions by discussion.

We independently assessed the full papers for methodological quality by extracting details of randomisation methods, blinding of treatments and assessments, whether intention-to-treat analysis was possible from the published data, whether treatment groups were comparable with regard to demographics and clinical characteristics, the number of patients excluded or lost to follow-up, definition of outcomes, and entry and exclusion criteria.

We looked for sources of bias including: (1) selection bias, including randomisation and chance differences in groups due to small sample sizes; (2) performance bias; (3) attrition bias; (4) detection bias; (5) selective reporting of results.

The reviewers noted compliance, dropouts and other exclusions from analysis. We classified the analysis of trials as being on the basis of "intention-to-treat", or not.

Two reviewers (Costa J, Ferreira JJ) independently abstracted eligible data onto standardised forms, crosschecked for accuracy and amalgamated them. We resolved disagreements about inclusion by discussion.

All results were expressed as ordinal data. The various rating scales used were dichotomised using each author's own criteria for improvement or no improvement. If these criteria were not described, we defined 'improvement' as any beneficial change from baseline and 'no improvement' as no improvement from baseline. We included any deterioration from baseline. In order to dichotomise the results, we requested individual patient data if the results were presented as mean values for groups.

We performed statistical analyses using the RevMan statistical software provided by the Cochrane Collaboration. We tested heterogeneity between trial results using a standard chi squared test. We reported the results as odds ratios (and 95% confidence intervals) for dichotomous outcomes and as weighted mean difference (and 95% confidence intervals) for continuous outcomes, using the Peto fixed effect method. We calculated the significance of any differences between odds ratios using a standard method (Altman 1996). Where we could not combine outcome data from different studies we gave a descriptive summary of the results.

RESULTS

Description of studies

See also: 'Characteristics of Included Studies'.

According to our inclusion criteria we were able to include just one study comparing anticholinergics with BtA. This study (Brans a)) was a randomised, multicentre, double-blind, double-dummy, two arms, parallel study, comparing trihexyphenidyl with BtA. It enrolled 66 patients (33 in each group) naïve to BtA with idiopathic cervical dystonia. Except for the higher frequency of patients with a history of progressive disease in trihexyphenidyl group, patients were well matched between both arms. The mean daily dose of trihexyphenidyl was 16.25 mg (range, 4 to 24).

BtA (Dysport(r), Ipsen) was injected under EMG guidance. The doses and selection of muscles to inject were based on the investigator clinical experience. Participants were injected at baseline (mean dose 292U: range, 38 to 440) and at week eight (mean dose 262: range, 36 to 440). It should be mentioned that in one centre five patients received half the planned BtA dose due to an error in dilution. Two participants, one in each group, dropped out of the study before receiving the study medication. One had a colon carcinoma and the other simply withdrew.

Several clinical tools are available for assessing and documenting the status of patients with spasmodic torticollis. Two of the most common used are the Tsui 1986 Scale and the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). The Tsui 1986 scale grades severity of postural deviance (rotatocollis, antecollis, retrocollis, head tilt, and elevation of shoulder), acknowledges the presence or absence of head tremor, as well as whether the movements are continuous or intermittent. The score ranges from 0 to 25, 25 corresponding to the maximum severity. It does not assess disability and pain. The TWSTRS scale (range, 0 to 85) is composed of 3 subscales that grade severity (range, 0 to 35), disability (range, 0 to 30), and pain (range, 0 to 20). It has been shown that Tsui 1986 and TWSTRS score reduction rates after Bt therapy correlated significantly with each other (Tarsy 1997).

The primary outcome of the study included in this review was change on the TWRTRS-Disability score at week 12. Secondary outcomes included the number of patients showing improvement of at least three points on the TWRTRS-Disability score, improvement of at least three points on the Tsui 1986 Scale, and global changes on the Tsui 1986 Scale, TWRTRS-Pain, and General Health Perception Subscale of the Dutch MOS-Quality of Life Scale (100-point scale, with 100 assigned as the best possible score). Adverse events data were collected through spontaneous reports.

We excluded one trial (Brans 1998b) done by the same authors and published two years latter. This study was a subgroup analysis of 42 participants that had been enrolled in the original study. The main outcome in this study was to compare EMG findings in cervical dystonia after trihexyphenidyl or BtA.

Risk of bias in included studies

The study we included assigned patients to treatment groups through a blinded independent randomization. It was double-blind and double-dummy. The high frequency of adverse events in the trihexyphenidyl group could have confounded the blinding in the trial. However, the assessments were made by a blinded investigator not involved in the treatment of the patients. They used an intention-to-treat analysis for the results. Reasons for withdrawals

were given. These methodological characteristics make it highly improbable that the study was subjected to selection, performance, attrition or detection bias.

Effects of interventions

We did not perform a meta-analysis as there was only one study. We present the results as Peto odds ratios (OR) for the number of patients who had various degrees of improvement together with the numbers need to treat (NNT) when differences were found, and as Weighted Mean Difference (WMD) for changes in objective scales scores. All outcomes were assessed at week 12.
For easier interpretation of Peto OR and WMD results we considered BtA as the treatment group and trihexyphenidyl the control group. Thus for both objective outcomes and adverse events values greater than 1 favour the BtA group.
Objective outcomes:
Change in objective scales: WMD (95% CI)
TWSTRS-Disability score (primary outcome): 2.50 (0.68 to 4.32)
Tsui 1986 score: 4.60 (2.14 to 7.06)
Number of patients with: Peto OR (95% CI); NNT
One point improvement in Tsui 1986 scale: 5.15 (1.93 to 13.79); 2.5
Three point improvement in Tsui 1986 scale: 3.92 (1.48 to 10.40); 2.9
One point improvement in TWSTRS-Disability scale: 3.11 (1.16 to 8.33); 3.6
Three point improvement in TWSTRS-Disability scale: 3.14 (1.10 to 8.97); 4
We could not determine WMD for change in the General Health Perception Subscale because the Standard Deviation (SD) was not given nor could we calculate it from the data available. However the authors gave the mean change (-4 in the trihexyphenidyl group, and +2 in the BtA group) and the level of significance for these difference in medians (p = 0.0023; 95% CI: 4 to 12). The authors commented that more participants in the BtA group experienced pain relief but did not give exact numbers. The mean improvement in TWSTRS-Pain scale score was one point in the trihexyphenidyl group, and three points in the BtA group. The SD for this difference was not provided, and according to the authors it did not reach statistical significance
Adverse events:
Adverse events data were collected through spontaneous reporting. There were no serious adverse events. Generally they were more common in patients treated with trihexyphenidyl than BtA (patients in the trihexyphenidyl and BtA groups experienced a total of 76 and 31 adverse events, respectively). The adverse events that were significantly different between groups favoured BtA, and are listed below, with the Peto odds ratios and numbers needed to harm (NNH).
Adverse event: Peto OR (95%CI); NNH
Dry mouth: 7.22 (2.72 to 19.12); 2.0
Forgetfulness: 3.51 (1.25 to 9.89); 3.6
Fatigue: 9.12 (1.92 to 43.30); 4.6
For all the other adverse events reported (blurred vision, dizziness, depression, disturbances of micturition, weight loss, dyspepsia, pain at injection site, dysphagia, neck weakness) there was no significant difference between trihexyphenidyl and BtA.

DISCUSSION

Quality of evidence

We were able to include only one trial and thus no meta-analysis was performed. This was a high quality trial in terms of internal validity producing clear results favouring BtA against anticholinergics. Although generalization of these results to the population is probably appropriate, there are some reasons to be cautious:

(1) Only few controlled data are available.

(2) The number of patients studied was relatively small.

(3) There were significant more patients with a history of progressive disease in the trihexyphenidyl group.

(4) The trial was short in duration, which may not favour trihexyphenidyl. In some patients it requires several weeks to achieve maximum benefit.

(5) BtA was injected twice in eight weeks, which is a shorter interval than the 12 to 16 weeks generally used in clinical practice.

(6) The median dose of BtA was half (262U) the dose used in the trials that compared BtA formulation Dysport with placebo (577U). It should be mentioned that five participants received half study dose due to a dilution error. The results for this group of patients did not differ significantly from the others.

There are no controlled data for any of the other anticholinergic drugs.

Findings

(1) Patient groups were in general appropriately selected and well matched except for gender and history of progressive disease. However there is no evidence for or against possible differential effects of gender or progressive nature of disease on the efficacy of Bt or trihexyphenidyl.

(2) On all objective and subjective rating scales measuring impairment, disability and handicaps BtA produced statistically and clinically significant improvements compared to trihexyphenidyl. The single exception to this was pain improvement, which did not reach statistical significance.

One recent review on the efficacy of BtA versus placebo in cervical dystonia produced Peto OR, NNT, and WMD that are generally

similar to the ones found in the present review. These findings suggest either a high placebo effect or a low effect for trihexyphenidyl. The results of the two systematic reviews are given below:

BtA versus Placebo; BtA versus Trihexyphenidyl

Change in objective scales:

Tsui 1986 score: WMD 2.1 (95% CI 0.7 to 3.4) versus WMD 4.6 (95% CI 2.1 to 7.1)

Number of patients with: (Peto OR, 95% CI) (NNT)

One point improvement in Tsui 1986 scale: 8.2 (4 to 17) (1.9) versus 5.2 (1.9 to 14) (2.5)

Three point improvement in Tsui 1986 scale: 4.3 (2 to 9) (2.9) versus 3.9 (1.5 to 10) (2.9)

Any improvement in Tsui 1986 or TWRTRS scale: 4.3 (3 to 7) (3.2) versus 4.1 (1.5 to 11) (2.9)

(3) BtA was better tolerated than trihexyphenidyl.

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence suggests that BtA injections provide more objective and subjective benefit than trihexyphenidyl to patients with cervical dystonia. We could not draw any conclusions about other anticholinergic drugs.

Implications for research

The efficacy and tolerability of BtA in cervical dystonia is well established. It is not reasonable to expect that future trials will be conducted to compare BtA with anticholinergic drugs. However they should explore the role of anticholinergic drugs in patients that do not get benefit with BtA.

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References to studies included in this review

Brans 1996 a ***{published data only}***

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Brans 1996 a

Methods	Randomised, multicenter, double-blind, 2 arms, parallel study.Method of randomisation: computer program.Data analysed on an intention-to-treat basis for all patients that receive any study medication.Location: 4 centers in Netherlands.Duration: 12 weeks
Participants	66 participants were enrolled.Trihexyphenidyl arm: 33 participants (1 withdrawal prior to receive study medication: 3%); 24 participants were female and 9 were male, mean age was 51.2 ± 12 (sd) years; ethnicity: not stated; mean duration of illness: 8.6 ± 6,8 (sd) years; 21 participants with course of disease of at least 5 years; 21 participants with a history of progressive disease; mean TWSTRS-Disability score at baseline: 15.8 ± 5.2 (sd); mean Tsui score at baseline: 14 ± 4.3 (sd), mean General Health Perception Subscale score at baseline: 67.3 ± 10.5 (sd).BoNT/A arm: 33 participants (1 withdrawal prior to receive study medication: 3%); 16 participants were female and 17 were male; mean age was 50.1 ± 11.9 (sd) years; ethnicity: not stated; mean duration of illness: 10.1 ±1 0.3 (sd) years; 23 participants with course of disease of at least 5 years; 9 participants with a history of progressive disease; mean TWSTRS-Disability score at baseline: 15.9 ± 5.4 (sd); mean Tsui score at baseline: 15.3 ± 4.3 (sd), mean General Health Perception Subscale score at baseline: 67.5 ± 10.8 (sd).Inclusion criteria: Idiopathic, mainly focal, Cervical Dystonia (CD) for at least 1 year; Informed consent.Exclusion criteria: age under 18 years; pregnancy; multifocal or generalized dystonia; other neurological disease, coagulation disorders, secondary dystonia; and previous treatment with BoNT/A
Interventions	The study drug Trihexyphenidyl (and equivalent placebo) was administered in tablets of 2 mg. The initial dose was one-half tablet daily, increased every 3 days to a maximum of 3 tablets four times daily (24 mg daily).The study drug BoNT/A (Dysport®) was diluted to 20U per 0,1mL of 0.9% sterile saline, and injected under EMG guidance. The selection of muscles to inject, the number of injection sites per muscle, and the volume per injection site were based on the investigator criteria. Participants were injected at baseline (mean dose 292U: range, 38 to 440) and at week 8 (mean dose 262: range, 36 to 440)
Outcomes	The primary efficacy outcome was the difference between the two treatment groups with regard to the change on the TWRTRS-Disability score. Secondary efficacy outcomes included: difference between the numbers of participants who had an improvement of at least three points on the TWRTRS-Disability score, difference between changes on the Tsui Scale, difference between the numbers of participants who had an improvement of at least three points on the Tsui Scale, difference between changes on the TWRTRS-Pain, and difference between changes on the General Health Perception Subscale of the Dutch MOS-Quality of Life Scale (100-point scale, with 100 assigned as the best possible score).For all outcomes data were collected at treatment visit (Week 0), and at week 12 (termination).Adverse events data were collected through spontaneously report
Notes	In one center 5 participants receive half of BoNT/A dose due to an error in dilution.Reasons for withdrawal: 2 participants discontinued the study, one in each group, before receiving the study medication, because of a colon carcinoma and withdrawal of cooperation

Risk of bias

Bias	Authors' judgement	Support for judgement

Brans 1996 a (*Continued*)

Allocation concealment?	Low risk	A - Adequate

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

Study	Reason for exclusion
Brans 1998b	This study is a subgroup analysis of the study included in the review. They have looked at EMG changes after BtA or trihexyphenidyl

WHAT'S NEW

Date	Event	Description
7 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 1, 2005

Date	Event	Description
8 October 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Protocol - Costa J, Miguel C, Ferreira JJ, Sampaio C

Literature search - Costa J, Borges A, Espírito-Santo C

Literature selection - Costa J, Borges A, Espírito-Santo C

Papers quality assessment - Costa J, Ferreira JJ

Data collection from papers - Costa J, Ferreira JJ

Interpretation of data - Costa J, Ferreira JJ, Moore P, Sampaio C

Review writing - Costa J, Ferreira JJ, Moore P, Sampaio C

DECLARATIONS OF INTEREST

Costa J, Ferreira JJ, Sampaio C, Moore AP, and Miguel C had been investigators in clinical trials sponsored by Elan, Allergan, and Ipsen. Ferreira JJ, Sampaio C and Moore AP were speakers in symposiums promoted by Elan, Allergan, and Ipsen.

INDEX TERMS

Medical Subject Headings (MeSH)

Botulinum Toxins, Type A [*therapeutic use]; Cholinergic Antagonists [*therapeutic use]; Neuromuscular Agents [*therapeutic use]; Torticollis [*drug therapy]

MeSH check words

Humans