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REVIEWS

Management of secretions in patients with severe neurological impairment - A systematic review

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Abstract
Background: Most children and young patients with severe neurological impairment of various etiologies have increased secretions in the respiratory tract. These, together with other predisposing factors, represent an important cause of morbidity, low quality of life and mortality.
There is a lack of consensus on the most effective interventions for the management of secretions in these specific patients.
Management methods are represented by: the use of anticholinergics, nebulization of hypertonic saline solutions followed by aspiration of secretions, injection of botulinum toxin, radiotherapy and surgical interventions on the salivary glands.
Purpose: The purpose of this literature review is to analyse methods of managing secretions in patients with neurological impairment, the main focus of the review being hyoscine butylbromide, a drug available in our country.
Summary: The systematic literature review analysed 56 studies, including 9 studies focused on anticholinergic treatment method in secretions management. The electronic search was performed on PUBMed and manually in the Cochrane Neuromuscular Specialized Register. The systematic literature review identified 5 *randomized controlled trials* (RCTs) and 4 observational studies, of which 4 RCT studies and 2 observational studies demonstrated the effectiveness of hyoscine in reducing secretions in patients with severe neurological impairment (p=0.089). Three of these showed that hyoscine, compared to glycopyrronium, has more side effects and is less likely to be tolerated by children and parents.
Conclusion: Hyoscine is effective in reducing secretions and does improve patients' quality of life, but side effects need to be considered when prescribing it.

Keywords: Hyoscine, Scopolamine, Scobutyl, Cerebral palsy, Neurological impairment, sialorrhea, management of secretions.

Rezumat
Background: Majoritatea copiilor și tinerilor cu deficit neurologic sever de diferite etiologii se confruntă cu secreții abundente la nivelul căilor respiratorii. Acestea, alături de alți factori predispozanți, reprezintă o cauză importantă de morbiditate, calitate scăzută a vieții și mortalitate.
Există o lipsă de consens cu privire la cele mai eficiente intervenții pentru gestionarea secrețiilor la aceşti pacienți.
Metodele de management sunt reprezentate de: utilizarea anticolinergicelor, nebulizarea soluțiilor saline hipertone, urmate de aspirația secrețiilor, injectarea cu toxină botulinică, radioterapia și intervențiile chirurgicale asupra glandelor salivare.
Scop: Scopul acestei revizii de literatură este de a analiza metodele de management a secrețiilor la pacienții cu deficit neurologic, principalul obiectiv al reviziei fiind bromura de butil de hioscină, un medicament disponibil în țara noastră.
Sumar: Revizia sistematică de literatură a analizat 56 de studii, dintre care 9 studii ce se axează pe metoda de tratament cu anticolinergice în gestionarea secrețiilor. Căutarea electronică a fost efectuată pe PUBMed și cea manuală in Cochrane Neuromuscular Specialised Register. Analiza sistematică de literatură a identificat 5 studii controlate randomizate (RCT) și 4 studii cantitative observaționale, dintre care 4 studii RCT și 2 studii observaționale au demonstrat eficiența hioscinei în reducerea secrețiilor bolnavilor cu deficite neurologice severe (p=0.089). Trei dintre acestea au arătat că hioscina, în comparație cu glicopirolatul are mai multe reacții adverse greu de tolerat, atât de către copii, cât și de către părinții acestora.

Cuvinte cheie: Hioscină, Scopolamină, Scobutil, Paralizie cerebrală, Deficit neurologic, sialoree, managementul secretiilor.

Introduction

A large part of pediatric palliative care beneficiaries are children and young patients with severe impairment of the central nervous system of various etiologies (cerebral palsy, mucopolysaccharidosis, Krabbe disease, progressive muscular dystrophy, Werdnig-Hoffman muscular atrophy, severe neurological sequelae of central nervous system infections).
These patients often have a number of predisposing factors for acute pneumonia (predilection for aspiration of saliva, food and fluids, increased secretions, ineffective coughing, gastroesophageal reflux, reduced mobility, malnutrition,

severe scoliosis, chronic airway carriage of pathogenic bacteria), leading to increased morbidity and mortality [1-4].
Respiratory failure is actually one of the most frequent causes of death in these children [5].
A study about the prevalence of pulmonary aspiration in 63 spastic tetraplegic children found that 56 % underwent aspiration causing infection [5, 6].
The management of increased secretions in these patients relies mainly on the experience of clinicians, as treatment evaluation studies are limited (few double blinded studies), have a small number of participants and are not designed for every disease [7].
Management methods include: use of anticholinergics, nebulization of hypertonic saline solutions followed by aspiration of secretions, botulinum toxin injection, radiotherapy and salivary glands surgery [8].
Airway-clearance therapy seems likely to be of benefit in the routine care of children with neuromuscular disease and cerebral palsy [9].
There is insufficient evidence to support the use of one intervention over another [10].
Hyoscine butylbromide (Scobutyl) is the anticholinergic we focus on in this systematic review, as it is the only anticholinergic drug that is available in our country.
It is most frequently used in palliative care services in managing death rattle [11-12].
The evidence supporting treatment of death rattle once it has begun is less clear, with no evidence that one antimuscarinic is clearly superior to another. There is no evidence that treatment of death rattle improves patient comfort [13].
Anticholinergic drugs are considered standard treatment for death rattle, although adequate placebo-controlled studies have not been performed [14].
Due to the fact that this therapeutic intervention is limited to a short period of time, long-term side effects are unknown.
There is also a similar paucity of evidence to support optimal management of increased secretions in other neurological conditions such as ALS. Few trials have been conducted in these patients and those that have are limited by their small numbers, lack of blinding and reliable outcome measures [15-17].
Therefore, the research question was: is it useful to administrate scobutyl to patients with severe neurological impairment for the management of secretions? What are the long-term side effects of this treatment?

Method
An electronic and manual search of literature was conducted, looking for studies that analysed methods of managing secretions in patients with severe neurological impairment.
The electronic search was carried out in the PUBMed electronic library and the manual search was performed in the Cochrane Neuromuscular Specialised Register.
For the electronic search, the following keywords, determined from a preliminary search of the PUBMed database, were used: ((hyoscine [MeSH Terms]) OR (scopolamine) OR (scobutyl)) AND ((neurological disorder [MeSH Terms]) OR (cerebral palsy [MeSH Terms] OR (drooling disorder))) AND ((drooling management [Mesh Terms]) OR (Secretion management)).
The electronic search mentioned above identified 56 studies.
The manual search found 5 studies.
Diagram of the selection process of relevant studies

- Potentially relevant studies after an exhaustive electronic database search (n=56). Potentially relevant studies after manual search (n=5)
- Studies excluded for certain reasons (n=52)
- Relevant studies included in the systematic review (n=9)

Study selection procedures and criteria

- Inclusion criteria: Primary studies were included, with no restriction on study design. The study population is patients with severe neurological impairment (amyotrophic lateral sclerosis, cerebral palsy) and terminally ill patients. The main inclusion criteria were the administration of hyoscine in at least one of the study groups. Another inclusion criteria were the use of hyoscine by the doctors surveyed in the descriptive studies.
- Exclusion criteria: Studies excluded because full-text could not be obtained (n=7), studies excluded because the intervention was not related to the administration of hyoscine (n=7), studies published before the year 2000 were excluded (n=5), studies excluded because the research object did not match the research question (n=23).
  Also excluded were studies with undefined research design (n=2) and studies with methods not clearly defined (n=2).

Assessing the quality of studies
The selected studies were mostly experimental studies and a few were quantitative observational studies.

- Data synthesis: 9 articles were included in the review
  - 5 RCT studies
  - 4 quantitative observational studies
  - 1 prospective observational controlled study
  - 1 cross-sectional descriptive study
  - 2 retrospective studies

The heterogeneity of the included studies is at the same time clinical, as the participants in the included studies have different characteristics: different diagnoses (cerebral palsy, amyotrophic lateral sclerosis, terminal cancer), different age groups (pediatric patients in the case of patients with cerebral palsy and adult patients in the case of patients with multiple sclerosis amyotrophic lateral sclerosis and end-stage cancer), as well as methodological (both experimental and observational studies were included).

Results
The review identified a total of 9 studies: 5 RCT studies and 4 observational studies.
4 RCT studies and half of the observational studies showed that Scobutyl is an effective method to decrease secretion in patients (Fig.1)

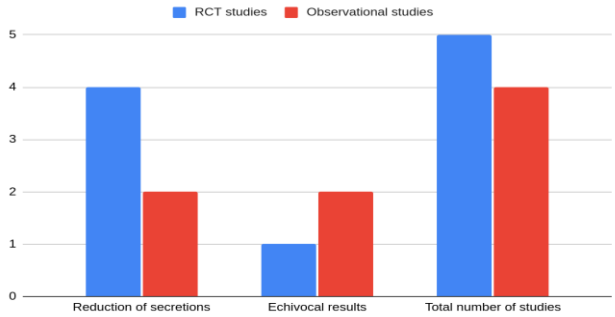

Figure 1 - Reduction of secretions after the administration of Hyoscine based on the study type

Most of the studies included in the systematic literature review reported favorable results following the use of anticholinergic medication for the management of secretions in patients with severe neurological impairment: 3 out of 4 studies (Fig. 2).
The controlled trial by Van der Burg JJ et al 2006 that included 54 children with cerebral palsy and severe sialorrhea, who received both hyoscine and botulinum toxin injected into the salivary glands, demonstrates a significant decrease in sialorrhea. The reduction of sialorrhea has significant positive effects on the patient's quality of life [18].
Jeremy R Parr et al, a 2017 RCT study that included 90 patients with neurological impairment with a mean age of 4 years (55 boys and 35 girls) compared the efficacy of hyoscine with that of glycopyrronium. A similar reduction in secretions was observed under treatment with both drugs. [19].
The 2010 RCT study by Mato et al examined the efficacy of reducing sialorrhea in 30 patients with neurological impairment after the administration of hyoscine patches. The study found a significant reduction in sialorrhea ($p<0.005$) in patients who received hyoscine compared to the control group at the first and second-week reassessments (69% and 80%, respectively). The study reports a 13% discontinuation rate due to side effects [20].
A cross-sectional descriptive observational study conducted by E. Chaleat-Valayer et al in 2015 observed the opinions of specialists related to the management of secretions in patients with cerebral palsy. A questionnaire was sent electronically to 401 specialists treating children with cerebral palsy. The most used method of management of secretions in France is physiotherapy (95% of professionals), followed by anticholinergic drugs (Scopolamine) (94%), botulinum toxin injections (66%) and surgery (34%). Scopolamine was considered less effective than botulinum toxin. Seventy-five percent of professionals reported side effects (22% reported their occurrence as "frequent"). Treatment was sometimes stopped because of side effects, according to 91% of respondents. [21]
In terminally ill patients, 2 out 2 studies showed the same results, while in ALS patients 2 studies out of 3 were echivocal (Fig. 2).
Odachi 2017 shows that the mean volume of saliva aspirated / day decreased under hyoscine patch use, but no significant differences were found between scopolamine and placebo treatment in terms of VAS change for severity($P=0.384$) or difficulty ($P=0.388$) [22].

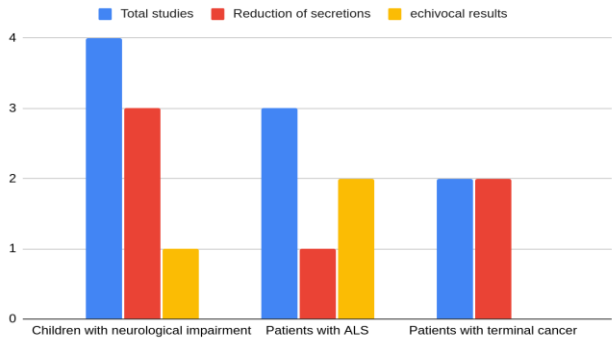

Figure 2 - Reduction of secretions after the administration of Hyoscine based on patient diagnosis

The majority of the studies included in this review reported side effects (7 out of 9) (Fig 3.). These side effects often lead to a discontinuation of the treatment. [20-21]. In the controlled trial by van der Burg 4 patients were removed from the study because of side effects [18].
Jeremy R Parr et al, a 2017 RCT study showed that patients were 42% more likely to continue treatment with glycopyrronium than with hyoscine, as the second drug is less tolerated by patients [19]. Out of the 9 studies included in this review, 3 compared hyoscine with glycopyrronium. All of them concluded that glycopyrronium has a better side effect profile [2,19, 23].
The 2 studies which did not report this discontinuation were those about managing death rattle, most probably because the therapeutic intervention is limited to a short time period.

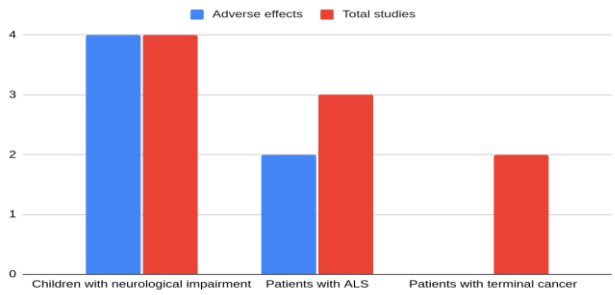

Figure 3 - Association of adverse effects of Hyoscine with patient diagnosis

Table 1 - Articles Summary

Author, year	The objective of the study	Diagnosis	Location of the patient	No. Part.	Study type	Medication	Result
Hughes A. Age of 2000	Evaluation of the effects of anticholinergics in the management of secretions	Terminal cancer	Hospice	37	Prospective study	Hyoscine hydrobromide Hyoscine butylbromide Glycopyrrolate	A smaller proportion of patients responded to the first dose of hyoscine hydrobromide (35%), compared to hyoscine butylbromide (54%) or Glycopyrrolate (46%).

Odachi 2017	Evaluation of the effectiveness of scopolamine patches in the management of sialorrhea in patients with amyotrophic lateral sclerosis	ALS	Unspecified	10	RCT	Scopolamine patches	The mean volume of saliva aspirated/day decreased under scopolamine patch use, but no significant differences were found between scopolamine and placebo treatment in terms of change in severity (P = 0.384) or difficulty (P = 0.388) scores.
E. Chaleat-Valayer et al 2015	Evaluation of the treatment of sialorrhea in children with cerebral palsy in France	Cerebral palsy	At home/in hospital	-	Descriptive cross-sectional observational study	Scopolamine patches Atropine Botulinum toxin injection Surgery Physiotherapy	The most used method of management of secretions in France is represented by physiotherapy (95% of professionals), followed by anticholinergic drugs (scopolamine) (94%), botulinum toxin injections (66%) and surgery (34%). Scopolamine was considered to be less effective than botulinum toxin
Ian N Back et al. 2001	Evaluation of the effectiveness of anticholinergics in the relief of death rattle	Terminal cancer	Hospice	204	RCT	In the first phase of the study all patients received Hyoscine hydrobromide as an anticholinergic, and in the second phase Glycopyrrolate was used	The number of patients with a reduced noise score that was observed after 30 minutes of administration of Hyoscine was greater compared to those in whom Glycopyrrolate was administered. (56% vs. 27%, P = 0.002). The need to administer an additional dose after 30 minutes was lower after administration of Hyoscine (33% vs 50%, P = 0.03).
Jan JW Van der Burg et al. 2006	Quality of life assessment of patients with cerebral palsy after sialorrhea treatment	Cerebral palsy	At home	45	RCT	Scopolamine patches Botulinum toxin injection	Significant reduction of sialorrhea following treatment with hyoscine patches: the symptom severity decreased by 35-40%, from 70-80 wipes of secretions per day, it reached 40-50 wipes, and from 7 bib changes to 4 changes per day

Mato 2010	Evaluation of the efficacy of transdermal scopolamine for the treatment of sialorrhea in patients with severe neurological impairment	Severe neurological impairment	Not specified	30	RCT	Scopolamine patches	Significant reduction in sialorrhea ($p<0.005$) in patients who received scopolamine compared to the control group at the first and second-week reassessments (69% and 80%, respectively) Severity of sialorrhea was assessed taking into account number of bibs used/day. This was found to decrease progressively during scopolamine treatment from 6 bibs/day at baseline to 4 bibs/day after the first week of treatment ($P < 0.005$) and at 3 bibs/day after the second week of treatment ($P < 0.005$).
McGeachan 2016	Identifying treatments that are currently prescribed. Specifying how experienced clinicians manage patients with treatment-resistant sialorrhea.	ALS	ALS Care Centers	119	Retrospective study	Hyoscine hydrobromide Hyoscine butyl bromide amitriptyline atropine propantheline, glycopyrrolate Botulinum toxin injections	An improvement in symptoms was recorded in 61% of patients receiving anticholinergics. Hyoscine patches have been the most commonly used therapy for sialorrhea. They were frequently associated with side effects (60%). The hyoscine patch discontinuation rate due to adverse effects was 33%. The use of glycopyrronium was generally preferred as a second-line treatment.
Jeremy R Parr et al 2017	Evaluation of effectiveness of hyoscine patch vs glycopyrronium syrup in the treatment of sialorrhea in children with neurological impairment.	Neurological impairment	At home	90	RCT	Hyoscine patch/ Glycopyrronium syrup	Both drugs significantly reduced sialorrhea at week 4. By week 12, only 55% of children who started hyoscine were still receiving it, compared with patients receiving glycopyrronium (82%).

Hobson et al 2012	Description of the most common practices for the management of sialorrhea in patients with ALS in the UK	ALS	ALS Care Centers	4 medical centers	Retrospective observational study	Atropine (drops) Glycopyrrolate Hyoscine patches Amitriptyline Botulinum toxin Carbocisteine radiotherapy	The drugs used as first line treatment were: hyoscine patches (65% of clinicians), amitriptyline (52%), carbocisteine (30%) and sublingual Atropine eye drops (26%) Hyoscine, botulinum toxin, atropine eye drops, amitriptyline and glyco- pyrolate were the most effective drugs for fluid secretions, and Carbocisteine and nebulization has been found to be effective for thick secretions. Atropine, carbocisteine, Glycopyrronium and botulinum toxin had the best side effect profile.

Discussions

The systematic literature review shows that, in general, anticholinergic medication is effective in the management of secretions. Several studies demonstrate that they reduce secretions, leading to an improvement in the patient's condition, and an increase in the quality of life for both, patients and their relatives. Also, some considerations related to the safety of their administration must be addressed, as the literature reports a series of side effects. [2,19-23]

Most of the studies were carried out for short periods of time, thus limiting the follow-up period of the side effects of the administered medication. As a result, no conclusions can be drawn about the long-term safety and long-term side effects of anticholinergics, as there are only a few case presentations with patients in whom they were used for a longer period of 3-5 months [24].

Therefore, we cannot exclude the occurrence of other side effects, which could exist if the treatment were prolonged.

Another limitation is that in most of the included studies, reporting of side effects (in patients with severe neurological impairment associated with communication difficulties, such as patients with cerebral palsy, for example) was done by their parents, and this may be underestimated for this reason [25-26].

The most frequent adverse reactions were represented by: xerostomia, constipation, acute urinary retention, local skin reactions (hyoscine patches), photophobia, drowsiness, hallucinations, confusional state (especially with anticholinergics administered orally) [27].

An important adverse reaction is represented by thickening of the respiratory secretions, an altogether more severe complication than sialorrhea itself [28]. In order to effectively manage the symptom, clinicians should consider the consistency of the excessive secretions.

As a result, physicians must carefully weigh the potential benefits of reducing secretions against the risks associated with these adverse reactions. Because anticholinergics are so commonly associated with adverse effects and symptom relief has been reported at relatively low doses, it is most appropriate to consider starting them at a low dose and titrating to the appropriate dose.

Of the 9 studies included in the review, 3 compared the administration of hyoscine butylbromide with glycopyrronium, presenting similar results: hyoscine has more frequent side effects than glycopyrronium, which is why patients receiving hyoscine drop out more often than those receiving the second anticholinergic [2, 22-23].

However, the use of scobutyl should be avoided in patients where the consciousness level or respiratory state is unstable, with hypercapnia [29].

Measuring saliva production or volume alone is unlikely to predict the level of distress caused by secretion problems [30].

An important aspect to consider is that the reduction of salivary flow should not be the only target in itself in the management of increased secretions. The question remains if the reduction of salivary flow does improve quality of life [31].

Anticholinergics are effective in reducing the amount of saliva and drooling, but data concerning the effect on respiratory status are missing [4].

Some of the studies included in this review also described the effects of botulinum toxin.

Even though botulinum toxin is not the therapeutic agent this review focuses on, it has to be mentioned that it seems to be more effective than scobutyl and also has fewer side effects [20,23]. A meta-analysis from 2021 showed that salivary botulinum toxin injection is a safe, reversible, effective treatment for drooling in children with cerebral palsy, with few adverse effects and no life-threatening events [32]. A review from 2015 described a decrease in hospitalized days, antibiotic

usage, and chest X-ray infiltrates after the salivary botulinum toxin injection in children with neurological impairment [33].
Another limitation of this systematic review is represented by the low number of studies performed on patients with severe neurological impairment, and the low number of subjects enrolled in these studies [34].
Future research should include well-controlled RCTs involving statistically significant numbers of patients, followed for a longer period of time, in order to evaluate the long-term safety and effectiveness of anticholinergic medication for management of secretions.

Conclusion

Scobutyl is effective in reducing secretions.
It has the potential to reduce symptoms, improve patients' quality of life.
The benefits must be carefully weighed against the potential risks, taking into account individual risk factors.
Future research should include well-controlled RCTs: statistically significant numbers of patients, followed for a longer period of time, to evaluate the long-term safety and effectiveness of anticholinergic medication for the management of secretions.
In addition, alternatives should be actively sought for patients who cannot tolerate this medication.

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