Intro to Research Principles - MiniCAT

Title: An examination of the efficacy of ipratropium bromide when administered in conjunction with salbutamol for treating asthmatic patients in comparison to the efficacy of only administering salbutamol.

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Clinical Scenario: A paramedic team responds to a call for a 23 year old male complaining of difficulty breathing and shortness of breath. The patient presents with wheezes when auscultated and while his vitals are generally stable the patient's ETCO2 reveals a mild 'shark fin' waveform. Recognizing the symptoms of an asthma attack, the paramedics decide to administer 800mcg of salbutamol through an MDI. They also administer 34mcg of ipratropium bromide via an MDI in an attempt to alleviate the bronchoconstriction.

PICO Question: For patients suffering from acute asthma attacks, is the administration of ipratropium bromide paired with salbutamol more effective in triggering bronchodilation and symptom relief than only administering salbutamol?

Relevance and Rationale of the Question: Currently, the anticholinergic drug ipratropium bromide (more commonly known as Atrovent) is not a medication prescribed under the Southwest Ontario Regional Base Hospital Program's Bronchoconstriction Medical Directive. However, a growing number of EMS services in the United States (such as Orange County EMS & Virginia Beach EMS) have implemented the drug into their bronchoconstriction guidelines. If it can be determined that ipratropium bromide is an effective medication when administered in conjunction with salbutamol then the drug could be introduced to Ontario's Life Support Directives.

Search Strategy:
("Ipratropium bromide" OR atrovent) AND (albuterol OR salbutamol) AND asthma AND (Comparative OR Comparison)

Search was limited to English language articles published within the last ten years. Search strategy was applied to Pubmed Database, CINAHL Database and the Fanshawe Library Journal Database (powered by the EBSCO Discovery Service)

Search Results: 27 Articles (See Appendix A for full details)

Relevant Papers: After removing duplicate and irrelevant articles, researcher was left with 5 articles for this miniCAT.

Please Note: For the sake of clarity and to minimize reader confusion, all references to 'albuterol' have been changed to 'salbutamol'.

Author, Date	Design / LOE	Population	Outcomes Measured	Results	Strengths & Weaknesses
Gelb et al., 2008 (2)	Outpatient, randomized, double-blind, single dose crossover study comparing salbutamol plus ipratropium bromide with salbutamol alone. Spirometry was performed on study participants to monitor improvements in forced expiratory volume. Spirometry was performed five minutes before and half an hour after treatment. Testing was conducted at 23 separate sites. LOE: I (Randomized Control Trial).	106 adults with moderate to severe asthma who had undergone corticosteroids treatment for at least a year before experiment began. Participants were all currently using salbutamol. All participants were currently non-smokers with a history of intensive smoking. Individuals were excluded for several serious conditions, such as recent intubation or myocardial infarctions. Patients had a mean age of 51.2, were mostly overweight and predominantly female. 39.8% of participants were African American, 2.7% were Asian and the remainder were Caucasian.	Average improvement in forced expiratory volume measured for one second (FEV1). Peak forced expiratory volume response. All outcomes measured three times. Highest measurement selected.	Study found the combination of ipratropium bromide plus salbutamol to be more effective than salbutamol alone. Patients given both medications had an FEV1 that was 72ml greater ($p = 0.0003$) and mean peak FEV1 was 55ml greater than control ($p = 0.0097$). The mean forced vital capacity response was 42ml greater ($p = 0.1521$) and mean peak FVC response was 15ml greater than control ($p=0.6544$). In addition, the study found that that the therapeutic response of participants who	*Strengths* Measuring FEV1 and Peak FEV is an excellent way to quantitatively measure how effective the medications were. Researchers maintained detailed statistics on population characteristics and pulmonary medication use to allow for subtype grouping. *Weaknesses* Excluded individuals who were too unhealthy. This makes the study less useful to paramedics in the field who don't have the privilege of only dealing with generally healthy patients. Study was funded by Boehringer Ingelheim Pharmaceuticals. This company produces several pharmaceuticals which utilize ipratropium bromide such as Combivent and Berodual.

				received ipratropium bromide plus salbutamol lasted twice as long as those who received just salbutamol (average of 245min as opposed to average of 106min for control)	
Kartininingsih et al., 2016 (3)	Randomized single blind controlled trial. Participants were randomized into two evenly sized groups. Group 1 received nebulized salbutamol. Group 2 received nebulized salbutamol and ipratropium bromide. Participants were assessed for two hours following medication and researchers monitored oxygen saturation and clinical asthma score. LOE: 1(Randomized Control Trial).	52 children aged 2-6 with acute asthma that had clinical scores between 5-10 (moderate asthma exacerbation). Children with mild or severe exacerbation were excluded from the study. Population was 60% male and one quarter of participants were identified as malnourished. Population drawn from pediatric emergency department of Soetomo Hospital, Surabaya.	Mean decrease in clinical asthma score during two hour observation period was principal outcome measured. Oxygen saturation percentage, number of nebulizations required, side effects and rates of admission to hospital were also measured.	Study found that ipratropium bromide plus salbutamol is more effective than salbutamol alone. Participants who received ipratropium bromide plus salbutamol had higher oxygen saturation and lower clinical scores during the two hour observation period ($p<0.05$) In addition, researchers found that participants who received ipratropium bromide in the	*Strength* Considered and measured ipratropium bromide side effects. Maintained statistics on relevant population medical history, including less common considerations such as malnourishment. Using pediatric patients in the emergency department allowed for researchers to see how the drug functioned when applied to real medicine as opposed to trials in a clinic. *Weaknesses* Article was originally published in 2006. Was only re-published in English in 2016.

				emergency department had a much lower rate of hospitalization than those who only received salbutamol but this result was not considered significant (*p>0.05)*	Test involved only 52 participants who were each only assessed once. Only assessed patients with moderate exacerbation, neglecting patients who scored higher than 10 on the Clinical Asthma Scale. Did not make use of spirometry tests to measure effectiveness of treatment.
Donohue et al., 2016 (1)	Randomized, double-blind, two-way crossover study. Patients were randomly assigned to two equal size groups. Group 1 received a dual ipratropium bromide / salbutamol medication while group 2 received only salbutamol. Patients were in charge of recording peak expiratory flow twice a day. Patients also	226 adult participants with physician diagnosed asthma for at least a year. All participants had a reduced FEV1 at the start of the trial. Patients with a history of COPD or other “significant” diseases were excluded from study. 57% of participants were female and the mean population age was 47 years old. 27% of the participants were	The key measurement of the study was FEV1 and peak FEV. The study also included asthma quality of life questionnaires, number of puffs taken daily, forced vital capacity, peak expiratory flow, night time	Greater bronchodilation was found in the participants who received the duel ipratropium bromide / salbutamol medication. Dual medicated patients had a FEV1 response of 252ml versus 167ml for control (*p<0.00001*) and a peak FEV1 response of 434ml versus control 357ml	*Strengths* Use of eDaries allowed participants to actively contribute to study and record findings daily. Relatively long term study that looked at large population. Made use of spirometry to quantitatively track measurements. *Weaknesses* Some data relied entirely on participants self reporting without a way for the researchers to

	received spirometry testing in clinic. LOE: 1 (Randomized Control Trial).	former smokers while the remainder had no history of smoking. Population was primarily Caucasian though 23% of participants were People of Colour.	awakenings due to asthma symptoms and several other measurements.	for control (*p=0.00001*). The duration of the bronchodilation was found to be twice as long in these patients. In addition, the participants also had a higher FEV1 response relative to their peers who only received salbutamol. No significant variation was found among the various subgroups accounted for in the study.	independently verify their eDiaries. Excluded overly unhealthy individuals with "significant" diseases. Many of the researchers had financial ties to Boehringer Ingelheim Pharmaceuticals, as well as a number of other pharmaceutical companies.
Leemans et al., 2010 (4)	Randomised, controlled, single-dose, four-way crossover animal trial. Participants were exposed to an allergen and then treated with either salbutamol, ipratropium bromide, salbutamol and ipratropium bromide or received no medication. Over the course of the study, each participant received all four treatments.	5 feline participants between 11 and 29 months of age with no history of respiratory tract infection in the last 6 weeks. Each participant demonstrated at least two phenotypes of feline asthma.	The primary outcome measured was based on *Penh.*It can be generally summarized that a higher *Penh* value was associated with poor breathing by the participant. Additional Recorded	Study found that participants who received any of the three medication options experienced a similar drop in *Penh* values (*p=0.00001*). There appeared to be no clinically significant difference between the ipratropium bromide plus	*Strengths* Study made use of a fairly ingenious design to measure bronchodilation in feline patients. Study made great use of a control group with the fourth placebo saline trial. *Weaknesses* Participants of study were cats with 'feline asthma'. As such, the study's findings likely have reduced relevance to the practice of paramedicine though they are

	Researchers took recordings of baseline of respiratory variables both at rest, after exposure to saline nebulization and after exposure to allergen. After the participants received either a medication or a placebo, their respiratory variables were checked seven times within two hours. LOE: 1 (Randomized Control Trial).		variables included respiratory frequency, inspiratory and expiratory times, estimated tidal volume and estimated minute volume. Several other variables were monitored.	salbutamol trial in comparison to the salbutamol trial. However, medications did reduce *Penh* values relative to the control placebo trial (*p=0.00001*).	assumedly of great interest to veterinarians. However, there are enough similarities between human and feline asthma that the lessons drawn from these animal trials are still at least somewhat clinically relevant. Study only involved 5 participants which is a very small sample size. Did not make use of spirometry or oxygen saturation measurement. However, these options may have been impossible or impractical given participant demographics.
Memon et al., 2016 (5)	Randomized controlled trial in which participants were split into two equal groups. Group A received 3 doses of nebulized salbutamol while Group B received ipratropium bromide in addition to 3 doses of nebulized salbutamol. Measurements were taken fifteen minutes after the	200 children 2-14 years old who visited an emergency room due to acute severe asthma. Mean population age was 9.2 and 56% of participants were male. Using the modified Bentur Clinical Score, 60% of participants were rated as having moderate asthma before receiving medication while 39% were	The primary outcome measured in this study was the participant's modified Bentur Clinical Score which determines the severity of an asthma attack. Other measured variables	93% of the participants who received ipratropium bromide in addition to salbutamol experienced a reduction in their clinical asthma scores. In comparison, only 84% of the participants who received just salbutamol experienced a drop in their	*Strengths* This study chose to include participants who were suffering from a severe asthma exacerbation in addition to moderate exacerbations. About two fifths of the participants in the study presented with a severe asthma exacerbation and this is a subgroup that should not be ignored when considered the efficacy of bronchodilator medication.

	third dose of salbutamol. LOE: 1 (Randomized Control Trial).	classified as having severe asthma exacerbation before receiving medication.	included heart rate and respiratory rate.	clinical asthma scores. However, the researchers believed that there was not sufficient statistical power to give these findings clinical significance (*p>0.05*)	Made use of a reasonably large sample size. *Weaknesses* Researchers failed to conduct a spirometry test on participants, both before and after administering medication. The researchers also failed to monitor oxygenation saturation during their observation of the patient. While the Bentur Clinical Scale is a useful tool to measure asthma exacerbation, it should should not be the only tool used for clinical studies.

Comments

- There appears to be a significant gap in the literature regarding the administration of ipratropium bromide in the prehospital environment, either in Canada or abroad.
- Most of the articles reviewed for this miniCAT made sure to include relatively diverse population samples regarding participant ethnicity and sex.
- There was a large body of work regarding the efficacy of ipratropium bromide that was excluded from this miniCAT due to the decision to only review papers published within the last ten years.

Impact of Findings to the Paramedic Practice:

This miniCAT does not provide enough evidence to justify introducing ipratropium bromide into the prehospital environment throughout Ontario. Of the five trials summarized in this paper, 1 was completed on animals, 2 made use of substandard measurements tools and 2 were conducted by researchers who were financially supported by companies who could stand to benefit from the introduction of ipratropium bromide into the prehospital setting. In addition, only 3 of the 5 studies provided evidence that the impact of ipratropium bromide was statistically significant in comparison to just salbutamol.

However, ipratropium bromide is a drug which merits further examination. While this miniCAT could not uncover evidence that ipratropium bromide administered with salbutamol is unequivocally more effective than salbutamol used singly, enough evidence has been laid out to justify further research into the matter. It should also be noted that anticholinergic medications are frequently used in the hospital environment in Ontario. In addition, the Prehospital Evidence Based Practice Database strongly recommends the use of anticholinergic medications for treating asthmatic patients (6). A countywide trial conducted by a single Paramedic Service could be a fantastic way to test the efficacy of the medication in the prehospital setting in a relatively cost effective manner.

Appendix A: Article Source Breakdown

CINHAL: 5 Articles Found with Search Strategy
2 Selected:
Donohue et al, 2016.
Gleb et al, 2008 was backchained through Donohue et al, 2016.

Pubmed: 11 Articles Found with Search Strategy, 0 Duplicates from CINHAL
2 Selected:
Memon et al, 2016
Leemans et al, 2009
1 Inaccessible
Hossian et al, 2013 (Appeared relevant to miniCAT, but researcher was unable to access full text)

Fanshawe Library Database: 12 Articles Found with Search Strategy, 1 Duplicate from CINHAL & Pubmed
1 Selected:
Kartininingsih et al., 2016

Appendix B: References

1. Donohue JF, Wise R, Busse WW, Garfinkel S, Zubek VB, Ghafouri M, et al. Efficacy and safety of ipratropium bromide/albuterol compared with albuterol in patients with moderate-to-severe asthma: a randomized controlled trial. BMC Pulmonary Medicine [Internet]. 2016 Dec [cited 2019 Mar 16];16(1).

2. Gelb AF, Karpel J, Wise RA, Cassino C, Johnson P, Conoscenti CS. Bronchodilator efficacy of the fixed combination of ipratropium and albuterol compared to albuterol alone in moderate-to-severe persistent asthma. Pulmonary Pharmacology & Therapeutics. 2008 Aug;21(4):630–6.

3. Kartinin ingsih L, Setiawati L, S MM. Comparison of clinical efficacy and safety between salbutamol-ipratropium bromide nebulization and salbutamol alone in children with asthmatic attack. Paediatrica Indonesiana. 2016 Oct 18;46(6):241.

4. Leemans J, Kirschvink N, Clercx C, Cambier C, Gustin P. Functional response to inhaled salbutamol and/or ipratropium bromide in Ascaris suum-sensitised cats with allergen-induced bronchospasms. The Veterinary Journal. 2010 Oct;186(1):76–83.

5. Memon B, Parkash A, Khan K, Gowa M and Bai C. Response to nebulized salbutamol versus combination with ipratropium bromide in children with acute severe asthma. Journal of Pakistan Medical Association. 66.3 (Mar. 31, 2016): p243.

6. EMSPEP Clinical Presentations Level of Evidence. [cited 2019Mar22]. Available from: https://emspep.cdha.nshealth.ca/LOE.aspx?VProtStr=Asthma&VProtID=200#Anticholinergic