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National treatment guidelines decreased use of racemic adrenaline for bronchiolitis in four Finnish university hospitals

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Running head: Impact of treatment guidelines on racemic adrenaline

CONFLICTS OF INTEREST

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Abstract

Aim: Inhaled racemic adrenaline was used for bronchiolitis in many hospitals in Finland prior to new national current care guidelines for bronchiolitis in 2014, which limited its recommendations to on-demand rescue therapy. We studied the drug's use before and after the new guidelines to gauge changes in prescribing habits.

Methods: This 2012-2016 study analysed how many 0.5 ml doses of racemic adrenaline were used for children by emergency rooms, paediatric wards and paediatric intensive care units at four university hospitals and estimated drug and staff costs.

Results: There were substantial differences in the yearly consumption of racemic adrenaline between the hospitals before and after the bronchiolitis guidelines were published, with reductions in drug costs and staff time. The overall use more than halved during the study period, particularly in two hospitals where baseline consumptions were highest, but not in a third where baseline consumption was already low. In the fourth, the baseline consumption was modest and there was a constant decrease during the study years.

Conclusion: The current care guidelines for bronchiolitis had some impact on clinical practice as the overall use of racemic adrenaline more than halved, but considerable differences remained in the four study hospitals after their publication.

Key notes

- We examined the use of racemic adrenaline in four Finnish university hospitals from 2012-2016, before and after 2014 when national current care guidelines on bronchiolitis limited its recommendations to on-demand rescue therapy.
- The overall use of racemic adrenaline more than halved, suggesting that the guidelines had an impact on clinical practice.
- However, we continued to find differences in its use between the hospitals before and after the guidelines were published.

Key words: bronchiolitis, clinical guidelines, prescribing patterns, racemic adrenaline, rescue therapy.

INTRODUCTION

Acute bronchiolitis is a common respiratory disease in infancy and in Nordic countries it is defined as the first episode of respiratory distress, with or without wheezing, before the age of 12 months (1). In contrast, the guidelines issued by the American Academy of Pediatrics in 2006 (2) and the UK's National Institute for Health and Care Excellence in 2015 (3) are based on an upper age limit of 24 months. The incidence of bronchiolitis is high in children under the age of one, with one in three presenting with mild-to-moderate bronchiolitis and 1-3% with severe bronchiolitis being treated in hospital (2,4).

The treatment of acute bronchiolitis has included inhalations of hypertonic saline, racemic adrenaline or salbutamol, inhaled or systemic corticosteroids and repeated suctioning of the airways. However, none of these interventions have proved to be effective (5-7) and none of the current guidelines on managing bronchiolitis recommend routine use of bronchodilators or corticosteroids (2,3). Cleaning the airways with suctioning is only useful if there is a lot of mucus in the respiratory tract and is not recommended when there is just mucosal swelling. Some research-based evidence has been published that suggests that inhaling racemic adrenaline may be useful in selected patients with bronchiolitis (8), but mainly as a rescue therapy (9). The cornerstones of the treatment for bronchiolitis are still monitoring breathing and feeding, and supplementary oxygen and fluid and ventilator support if needed.

In the summer of 2014, national evidence-based current care guidelines for treating infant bronchiolitis and other lower respiratory tract infections in children were published in Finland (10).

These guidelines did not recommend the use of racemic adrenaline for the routine treatment of acute bronchiolitis, but stated that it could be used as an on-demand rescue therapy.

In children`s hospitals, the only common indication for the use of racemic adrenaline in recent years has been acute bronchiolitis (1). Other less common uses have included treating acute laryngitis, acute severe asthma and as a rescue therapy for laryngeal spasms during, or after, intubation.

Although different evidence-based guidelines are now being published more frequently in many countries, their effectiveness has been insufficiently studied (11). However, a 2017 study reported that the implementation of the UK bronchiolitis guidelines, which were published by the National Institute for Health and Care Excellence in 2015 and supported by a simple educational intervention, reduced the number of chest radiographs and antibiotics prescribed for bronchiolitis (12). In the USA, the publication of the 2006 American Academy of Pediatrics bronchiolitis guidelines was associated with reductions in the use of resources, including chest radiographies, bronchodilators and corticosteroids (13).

The aim of this study was to evaluate the impact of the 2014 Finnish evidence-based current care guidelines on the treatment of bronchiolitis in four university hospitals in Finland. The consumption of racemic adrenaline was assessed each year from 2012 to 2016, before and after publication of the national guideline on the treatment of bronchiolitis in 2014.

MATERIAL AND METHODS

This study evaluated the consumption of racemic adrenaline in the paediatric departments of four Finnish University Hospitals - Kuopio, Oulu, Tampere and Turku – by using hospital pharmacy records. We estimated the consumption based on the numbers of doses of racemic adrenaline (racepinephrine 2.25% 0.5 ml) that the hospital pharmacies delivered to the paediatric departments

of the hospitals. As well as analysing total consumption, we obtained detailed information on the amount used by the different paediatric units, such as the paediatric emergency room, the paediatric infectious disease ward and the paediatric intensive care unit (PICU).

Cost data on the actual drugs were obtained from the pharmacy at Tampere University Hospital and we used other data from the hospital on associated factors, such as staff time. All the costs were evaluated using 2017 prices and were reported as Euros. The doses of racemic adrenaline cost €2.30 each. The nurses' time was evaluated in hours and their salaries were not taken into account in the cost calculations. We estimated that it took 10 minutes to check the doctor's order, prepare the drug and solution ready for use and give the nebulised drug to the infant. This time was under-estimated rather than over-estimated and any time taken to reassure the infant was not included, although it was often needed.

The numbers of infants under the age of 12 months admitted for bronchiolitis to the paediatric emergency room of Tampere University Hospital were available from the hospital's electronic files for 2013-2015 and they were 238 in 2013, 213 in 2014 and 172 in 2015. The bronchiolitis diagnoses were confirmed with revisiting the patient records. According to the national Register for Infectious Diseases, the total number of laboratory-confirmed respiratory syncytial virus (RSV) infections in Finland was 4947 in 2016, compared to 1991, 2868 and 2436 in 2013, 2014 and 2015, respectively (14).

In addition we retrieved Government data on the number of children under 16 years of age covered by the four hospital districts and these were: Tampere (91,010), Oulu (88,094), Kuopio (26,518) and Turku (78,641) (15).

The consumption of racemic adrenaline was expressed as crude numbers of consumed doses and as the number of consumed doses per 10,000 children aged less than 16 years in the population.

RESULTS

There were substantial differences in the yearly consumption of racemic adrenaline between the four university hospitals both before and after publishing of the bronchiolitis guideline (Table 1).

There was also a significant decrease in the annual use of racemic adrenaline between 2012-2013 and 2015-2016 in Kuopio and Tampere, but not in Oulu where the baseline consumption was already low (Table 1). In Turku, the baseline consumption was modest and there was a constant decrease during the study years (Figure S1). The highest consumption in 2012 was in Tampere (3,295), followed by Kuopio (2,283), Turku (1,135) and Oulu (468), but this had fallen by just over 54% in 2016 and the order had changed to Kuopio (1,373), Tampere (773), Oulu (650) and Turku (326). When the rates were presented per 10,000 children under the age of 16 in 2012 and 2016, they were 846 and 734 in Kuopio, 366 and 85 in Tampere, 144 and 42 in Turku and 56 and 74 in Oulu. The overall reduction in the use of racemic adrenal across the four hospitals during the study period was just over 54%.

In 2012-2013, when the consumption of racemic adrenaline was common in Tampere and Kuopio, two-thirds of the consumption was in paediatric wards handling infection diseases. This was mainly due to the fact that the most common cause for hospitalisation was bronchiolitis and those patients were given racemic adrenaline inhalations. Although, the indications in the emergency room and PICU showed more variations, bronchiolitis was also the most common disease treated with racemic adrenaline.

The numbers of children admitted to the emergency room of hospital for bronchiolitis were available from Tampere, and the numbers of doses delivered from the hospital pharmacy per an admitted child were 14.7 in 2013, 11.5 in 2014 and 4.5 in 2015. In 2016, when there was a severe

RSV epidemic in Finland, the total numbers of laboratory-confirmed RSV infections were 2.5-fold, 1.7-fold and 2.0-fold higher than in 2013, in 2014 or in 2015, respectively.

The annual medication costs tended to be stable in Oulu and Kuopio and decreased in Tampere and Turku, reflecting changes in their use of racemic adrenaline. In 2012, the annual costs varied from €7,579 to €1,116 and in 2016 they varied from €3,158 to €750 (Table 2). Another notable expense was the time that the nurses spent preparing the medicines and solutions ready for use and administering the nebulised medicines to the infants. In 2012, the annual working time varied from a total of 186 to 1,263 hours for the four hospitals and in 2016 it varied from 125 to 526 hours (Table 2). The largest decrease, of 967 hours or 25.3 working weeks, occurred in Tampere. Other expenses that should be taken into account, apart from the cost of each drug dose (€2.30), were the two needles and two syringes required for one dose of racemic adrenaline (total €0.15), 2mL of normal saline solution per dose (€0.03) and the pro-rata purchase price and servicing of the nebuliser (€2.38) for each dose. These repeated costs €2.48 per dose, depended on the number of racemic adrenaline doses that were used. In 2012, the repeated costs ranged from €1,193 to €8,106 and in 2016 they ranged from €802 to €3,378.

DISCUSSION

Racemic adrenaline inhalations have been widely used in the Nordic countries to treat bronchiolitis (1,9). The accumulating evidence against the routine use of adrenaline (2,9), meant that its use was not recommended for clinical practice when the Finnish evidence-based current care guidelines were published in 2014 (10). This study was conducted to evaluate the impact of these guidelines on clinical practice comparing the two years before and after their introduction.

There were three key results that emerged from our study. First, the use of racemic adrenaline decreased substantially after the Finnish guidelines were published, based on the number of doses delivered by pharmacies to the departments in the four university hospitals. Second, although the use of racemic adrenaline fell after the guidelines were published, its use continued to vary considerably between the hospitals, especially with regard to the population-based analyses. Third, the medication costs were relatively modest, but time that the nurses spent administering racemic adrenaline showed a notable decrease. These results suggest that the evidence-based current care guidelines contributed to real-life treatment practice.

In the present study, the greatest decrease in the consumption of racemic adrenaline was mainly seen, as expected, in the hospitals that used the greatest quantities before the guidelines were issued. In the USA, the overall consumption of bronchodilators in bronchiolitis decreased modestly, from 70% to 58% in 2008-2012, after the 2006 American Academy of Pediatrics guidelines on the management of bronchiolitis were published. However, the figures for racemic adrenaline were not given separately (16). In hospitalised children in the USA, the use of racemic adrenaline for bronchiolitis decreased from 17.8% in 2004-2005 to 12.2% in 2007-2008 (17). On the other hand, some reports concluded that the use of bronchodilators remained stable after implementation of the 2006 guidelines, both in ambulatory and hospital settings (18,19). A study published in 2017, reported that, following the publication of the 2015 guidelines on managing bronchiolitis by the UK's National Institute for Health and Care Excellence, a secondary paediatric unit in England performed an educational intervention and the use of salbutamol decreased from 36% to 24%. However, the authors pointed out that racemic adrenaline was not used by this hospital, either before or after 2015 (12).

The use of racemic adrenaline varied a lot between the four university hospitals in our study. A study of three of the four Finnish university hospitals featured in the current study was carried out in 2008-2010, and substantial variation was observed in terms of other diagnostic and treatment practices for bronchiolitis, such as the use of salbutamol inhalations, systemic corticosteroids or

intravenous versus oral fluid therapies (20). Notable variations that cannot be explained by disease severity or readmission rates, have been reported from the USA and Spain (19,21,22). Furthermore, the use of unnecessary treatment, such as bronchodilators, antibiotics and corticosteroids, has been associated with longer stays in hospital in the USA (19).

A retrospective time series study from the USA revealed that, after the implementation of the American 2006 bronchiolitis guidelines, the average total costs per patient fell by $197 in the emergency room (23). This reduction was based on the decreased use of chest radiographs and tests for viruses, as well as reductions in the medication used. Our study identified reductions in the medication costs and the time spent by the nurses who prepared and gave the inhalations of racemic adrenaline. In Tampere, the nurses' annual total working time decreased by 967 hours from 2012 to 2016, which was the equivalent of six months for one nurse working full time. The reduction meant that nurses were free to carry out other duties in these busy departments.

The impact that evidenced-based guidelines and clinical practice guidelines have on everyday practice remains unclear (11,24). A prospective closed-loop audit study performed in the UK reported significant improvement in clinical practice after treatment guidelines were issued on the treatment of pneumonia (25). Meanwhile a multicentre voluntary collaboration of 21 American primarily community hospitals found that a web-based initiative that included data collection and feedback to doctors on bronchiolitis resulted in a 29% reduction in the use of bronchodilators, a 68% reduction in the use of corticosteroids and a 44% reduction in chest radiography (26). In Finland, a limited number of doctors treat infants with bronchiolitis, which means that the implementation of the guidelines in the study hospitals was probably easier than in the case of many other illnesses or in other settings than hospitals with specific paediatric expertise. Our study showed that a certain level of harmonisation can be achieved between hospitals when national guidelines are issued. However, educational or other interventions may be needed, because significant differences in the treatment of bronchiolitis still existed, even between the university hospitals in our study, after implementing the national guidelines.

The main strength of the study was that the results were based on real consumption figures at the different paediatric units of the four university hospitals and the figures were obtained from the hospital pharmacies. However, the study had two main limitations. Firstly, no data was available to indicate why the racemic adrenaline was given to the patients, namely specific diseases and indications. We only estimated that most of the inhalations on the paediatric infection wards were given to bronchiolitis patients. Croup very rarely needs in-patient treatment in hospital (27) and patients with asthma are hospitalised less than earlier and those hospitalised with severe asthma are usually treated in an intensive care unit (28). In any case racemic adrenaline is only a rescue therapy for severe asthma and it is needed very rarely. Secondly, the figures were only obtained from four university hospitals and the use of racemic adrenaline in secondary-level hospitals as well as in out-patient clinics, remains unclear. However, the hospitals we studied covered more than 30% of the child population in Finland.

CONCLUSION

We found some evidence that the 2014 Finnish evidence-based clinical care guidelines on the treatment of bronchiolitis had an impact on the everyday clinical care of children with regard to reducing the use of racemic adrenaline. They also had some impact on the amount of nursing time spent preparing and administering this treatment and reduced the already modest drugs costs. Future studies should focus on the impact that evidence-based current care guidelines have on children, including assessing cost effectiveness. Maybe such monitoring should be part of producing and updating any guidelines.

Abbreviations

PICU, paediatric intensive care unit

References:

1. Mecklin M, Hesselmar B, Qvist E, Wennergren G, Korppi M. Diagnosis and treatment of bronchiolitis in Finnish and Swedish children's hospitals. *Acta Paediatr* 2014;103:946–50.
2. Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2014;134:e1474-1502.
3. National Institute for Health and Care Excellence. Bronchiolitis : diagnosis and management of bronchiolitis in children. Http://WwwNiceOrgUk/Guidance/Ng9 [Internet]. 2015 [cited 2017 Oct 12];1–301. Available from: https://www-ncbi-nlm-nih-gov.helios.uta.fi/pubmed/26065055
4. Angoulvant F, Bellêttre X, Milcent K, Teglas JP, Claudet I, Le Guen CG, et al. Effect of nebulized hypertonic saline treatment in emergency departments on the hospitalization rate for acute bronchiolitis: A randomized clinical trial. *JAMA Pediatr* 2017;171:e171333.
5. Fernandes RM, Bialy LM, Vandermeer B, Tjosvold L, Plint AC, Patel H, et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane database Syst Rev* 2013;6:CD004878.
6. Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. *Cochrane database Syst Rev* 2014;6:CD001266.
7. Maguire C, Cantrill H, Hind D, Bradburn M, Everard ML. Hypertonic saline (HS) for acute bronchiolitis: Systematic review and meta-analysis. *BMC Pulm Med* 2015;15:148.
8. Plint AC, Johnson DW, Patel H, Wiebe N, Correll R, Brant R, et al. Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med* 2009;360:2079–89.
9. Skjerven HO, Hunderi JO, Brugmann-Pieper SK, Brun AC, Engen H, Eskedal L, et al. Racemic adrenaline and inhalation strategies in acute bronchiolitis. *N Engl J Med* 2013;368:2286–93.
10. Tapiainen T, Aittoniemi J, Immonen J, Jylkka H, Meinander T, Nuolivirta K, et al. Finnish guidelines for the treatment of laryngitis, wheezing bronchitis and bronchiolitis in children. *Acta Paediatr* 2016;105:44–9.

11. Giguère A, Légaré F, Grimshaw J, Turcotte S, Fiander M, Grudniewicz A, et al. Printed educational materials: effects on professional practice and healthcare outcomes. In: *Cochrane Database of Systematic Reviews* [Internet] 2012 [cited 2018 Jan 21]. p. CD004398.
12. Breakell R, Thorndyke B, Clennett J, Harkensee C. Reducing unnecessary chest X-rays, antibiotics and bronchodilators through implementation of the NICE bronchiolitis guideline. *EurJ Pediatr* 2017; 177: 47-51.
13. Parikh K, Hall M, Teach SJ. Bronchiolitis management before and after the AAP guidelines. *Pediatrics* 2014;133:1-7.
14. Register for Infectious Diseases, Institute of Health and Well-being, Finland [Internet] [cited 2018 Apr 15]. Available from: https://thl.fi/en/web/infectious-diseases.
15. Statistics on wellfare and health in Finland [Internet] [cited 2018 Feb 25]. Available from https://www.sotkanet.fi/en/index.
16. Ralston S, Garber M, Narang S, Shen M, Pate B, Pope J, et al. Decreasing unnecessary utilization in acute bronchiolitis care: results from the value in inpatient pediatrics network. *J Hosp Med* 2013;8:25–30.
17. McCulloh RJ, Smitherman SE, Koehn KL, Alverson BK. Assessing the impact of national guidelines on the management of children hospitalized for acute bronchiolitis. *Pediatr Pulmono*l 2014;49:688–94.
18. Johnson LW, Robles J, Hudgins A, Osburn S, Martin D, Thompson A. Management of bronchiolitis in the emergency department: impact of evidence-based guidelines? *Pediatrics* 2013;131 Suppl:103.
19. Florin TA, Byczkowski T, Ruddy RM, Zorc JJ, Test M, Shah SS. Variation in the management of infants hospitalized for bronchiolitis persists after the 2006 American Academy of Pediatrics bronchiolitis guidelines. *J Pediatr* 2014;165:786-92.e1.
20. Elenius V, Bergroth E, Koponen P, Remes S, Piedra PA, Espinola JA, et al. Marked variability observed in inpatient management of bronchiolitis in three Finnish hospitals. *Acta Paediatr* 2017;106:1512–8.

21. Sangrador CO, de Dios JG, of the aBREVIADo Project (Bronchiolitis--Study of Variability Adequacy, Adherence). Management of acute bronchiolitis in emergency wards in Spain: variability and appropriateness analysis (aBREVIADo Project). *Eur J Pediatr* 2012;171:1109–19.
22. Macias CG, Mansbach JM, Fisher ES, Riederer M, Piedra PA, Sullivan AF, et al. Variability in inpatient management of children hospitalized with bronchiolitis. *Acad Pediatr* 2015;15:69–76.
23. Akenroye AT, Baskin MN, Samnaliev M, Stack AM. Impact of a bronchiolitis guideline on ED resource use and cost: a segmented time-series analysis. *Pediatrics* 2014;133:e227-34.
24. Mittal V, Darnell C, Walsh B, Mehta A, Badawy M, Morse R, et al. Inpatient bronchiolitis5guideline implementation and resource utilization. *Pediatrics* 2014;133:e730-7.
25. Clements H, Stephenson T, Gabriel V, Harrison T, Millar M, Smyth A, et al. Rationalised prescribing for community acquired pneumonia: A closed loop audit. *Arch Dis Child* 2000;83:320–4.
26. Ralston SL, Garber MD, Rice-Conboy E, Mussman GM, Shadman KA, Walley SC, et al. A Multicenter Collaborative to Reduce Unnecessary Care in Inpatient Bronchiolitis. *Pediatrics* 2016;137:e20150851.
27. Tyler A, McLeod L, Beaty B, Juarez-Colunga E, Birkholz M, Hyman D, et al. Variation in Inpatient Croup Management and Outcomes. *Pediatrics* 2017;139:e20163582.
28. Kivistö JE, Protudjer JLP, Karjalainen J, Bergström A, Korppi M. Trends in paediatric asthma hospitalisations - differences between neighbouring countries. *Thorax* 2018;73:185–7.

Table 1. The number of doses of racemic adrenaline (2.25%, 0.5ml inhalation solution) delivered from the pharmacies to the paediatric department in the four Finnish university hospitals. The data are presented separately for the emergency room (ER), paediatric infectious diseases ward (ward) and paediatric intensive care unit (PICU) of each hospital during 2012-2016.

Hospital	**Unit**	**2012**		**2013**		**2014**		**2015**		**2016**	
Tampere	Total*	3,295	366	3,498	388	2,460	270	780	85	773	85
	ER	870		738		630		210		293	
	Ward	2,125		2,400		1,350		450		330	
	PICU	300		360		480		120		150	
Oulu	Total*	485	56	672	77	648	74	537	61	650	74
	ER^	-		-		-		-		-	
	Ward	230		291		240		248		325	
	PICU	155		251		270		185		210	
Turku	Total*	1,135	144	689	88	560	71	490	63	326	42
	ER	280		417		110		30		146	
	Ward	290		120		330		310		145	
	PICU	270		150		60		116		30	
Kuopio	Total*	2,283	846	2,745	1,035	2,333	880	1,919	734	1,373	532
	ER	367		286		324		260		270	
	Ward	1,625		1,894		1,709		1,305		920	
	PICU	79		55		25		23		53	

*Total doses of racemic adrenaline (racepinephrine) and doses per 10,000 children aged less than 16 years. ^ The ER costs were included in the ward costs and could not be obtained separately.

Table 2. The costs of racemic adrenaline (racepinephrine 2.25% 0.5ml inhalation solution) and working time of nurses (in hours) used for administering nebulisation in four university hospitals in Finland during the years 2012-2016. In Finland, the regular working time of nurses is 38.25 hours per week.

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	2012	2013	2014	2015	2016
Tampere					
costs (€)	7,579	8,045	5,658	1,794	1,778
working time (h)	1,263	1,341	943	299	296
Oulu					
costs (€)	1,116	1,546	1,490	1,235	1,495
working time (h)	186	258	248	206	249
Turku					
costs (€)	2,611	1,585	1,288	1,127	750
working time (h)	435	264	215	188	125
Kuopio					
costs (€)	5,251	6,314	5,366	4,414	3,158
working time (h)	875	1,052	894	736	526

Supplementary Figure 1. The annual consumption of racemic adrenaline in four university hospitals in Finland in years 2012-2016 (racepinephrine *2.25%* 0.5ml doses). The lower graph shows the consumption adjusted to doses per 10,000 children under the age of 16 years.