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List Of Abbreviations

CRS = chronic rhinosinusitis

CRSsNP = chronic rhinosinusitis without nasal polyps

CRSwNP = chronic rhinosinusitis with nasal polyps

AERD = Aspirin-exacerbated respiratory disease

NSAIDs = non-steroidal anti-inflammatory drugs

CAST = cellular activation stimulation test assay

Cys-LT = cysteinyl leukotriene

Abstract

Statement of problem

Topical corticosteroids nasal sprays remain first line of treatment for patients with chronic rhinosinusitis (with or without nasal polyps). The main aim of treatment is to improve nasal symptoms by reducing or eliminating the nasal polyps[1] and preventing polyp recurrence post-operatively[2–6]. Our aims were to determine if the type of corticosteroid nasal spray used post operatively influences polyp recurrence rate and if there were any subsequent economic implications as we only have beclomethasone available for prescription in our state hospital.

Methods

Retrospective case note review of all Samter's patients who underwent fronto-spheno-ethmoidectomy by a single surgeon (2000 – 2014).

Results

58 patients were included in our study, divided into 3 study groups. When compared to patients using beclomethasone; patients using fluticasone had an 80% reduced risk of polyp recurrence and patients using mometasone a 90% reduced risk. This rose to 88% and 96% respectively when adjusted for age.

Conclusion

Fluticasone and mometasone are both statistically significantly more effective at reducing polyp recurrence than beclomethasone in our population group. Mometasone appeared more effective than fluticasone, but this difference was not statistically significant.

PART A: RESEARCH PROTOCOL

Comparing the efficacy of various corticosteroid nasal sprays in a Samter's population

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Introduction

The exact aetiology for chronic rhinosinusitis with nasal polyposis (CRSwNP) is largely unknown, possibly because a single, unified cause may not exist[7].

Samter's triad, also commonly referred to as, Aspirin-exacerbated respiratory disease (AERD) is an acquired chronic inflammatory disease characterised by CRSwNP, asthma and airway reactivity to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs)[8]. The disorder is caused by an anomaly in the arachidonic acid cascade, which causes overproduction of leukotrienes, a series of chemicals involved in the body's inflammatory response. Patients typically present in their 20's to 30's and often require multiple operations for nasal polyposis which are notoriously aggressive and have a tendency to recur[9–13].

Topical corticosteroids in the form of nasal sprays remain the first line of treatment of patients with chronic rhinosinusitis with or without nasal polyps[1,14,15]. The main aim of treatment is improve nasal symptoms by reducing or eliminating the nasal polyps[1]. They also have an essential role in preventing polyp recurrence should surgical intervention be required[2–4]. Numerous different corticosteroid nasal spray preparations are available but there is no consensus on which is most efficacious.

Justification

Beclomethasone nasal spray is the only corticosteroid nasal spray available for prescription at Groote Schuur Hospital (state funded). We set out to compare the efficacy of beclomethasone to other available corticosteroid nasal sprays (fluticasone and mometasone).

We conducted a retrospective case-note review of all Samter's patients undergoing fronto-spheno-ethmoidectomy; documenting the time taken to notice endoscopically visualised polyp recurrence and the nasal preparation used.

Our hypothesis is that beclomethasone nasal spray is less effective at reducing the polyp recurrence rate in Samter's patients when compared to other nasal sprays and should be replaced by more efficacious preparations on the state formulary.

Aims & Objectives

Aims

1. To compare the efficacy of various steroid nasal sprays at reducing polyp recurrence
2. To compare the efficacy of generic versus non-generic nasal sprays
3. To determine any cost implications

Objectives

- To determine whether nasal polyps had recurred on nasal endoscopy following fronto-spheno-ethmoidectomy at post-operative visits
- To determine which nasal spray had been used post-operatively

Research Design & Methods

Study design

Retrospective case note review of all patients identified as Samter's patients who had undergone fronto-spheno-ethmoidectomy for polyposis by a single surgeon in both her private and public health practices.

Inclusion criteria

- Confirmed hypersensitivity reaction to Aspirin or other non-steroidal anti-inflammatories, asthmatic with nasal polyposis
- Undergone fronto-spheno-ethmoidectomy
- Single surgeon
- Minimum of 6 months follow-up post-operatively (unless polyps noted to recur within 6 months)

Exclusion criteria

- Less than 6 months follow-up (unless polyps noted to have recurred)
- Non-compliance with nasal spray
- Changed nasal spray between post-operative follow-up visits

Data collection

- Age
- Gender
- Number of previous FESS surgeries (all surgeons)
- Date of fronto-spheno-ethmoidectomy by single surgeon
- Hospital
- At post-operative follow-up visits:
    - Date of visit
    - Have nasal polyps recurred (on nasendoscopy)
    - Nasal spray used and compliance
    - Change of nasal spray
    - Sense of smell present

Analysis

Using the data collected; the time taken to notice polyp recurrence could be calculated for each nasal spray and documented as a treatment failure. If no recurrence is noted on endoscopy, then the time is calculated since surgery and documented as a non-failure for that nasal spray. Stata12 was used for statistical analysis of Kaplan-Meier survival.

Population

All patients with a confirmed hypersensitivity reaction to Aspirin or other non-steroidal anti-inflammatories, who are asthmatic and have nasal polyposis (Samter's patients) who underwent fronto-spheno-ethmoidectomy by a single

surgeon at either Groote Schuur Hospital or Panorama Hospital between 2004 and 2014 and had at least 6 months post-operative follow-up period (unless their polyps recurred within 6 months).

Sampling

The folder numbers of all Samter's patients who underwent fronto-spheno-ethmoidectomy at Groote Schuur Hospital and Panorama Hospital between 2004 and 2014 were obtained from surgery logbooks. Their medical records were then recalled and analysed.

Sample size

58 patients

Ethical Considerations

Confidentiality

The identity of the patients in the study were protected during the collection, analysis and reporting of data by making use of the hospital folder numbers. Only the principle investigator and other investigators on the study had access to the medical records and collected data.

Beneficence

The study will serve as an audit of the efficacy of various steroid nasal sprays. This will enable patients to be accurately informed of the relative risk of their nasal polyps recurring post-operatively and by implication the risk of future potential sinus surgery. The study will also widen the scope of epidemiological research in that the results can be used to modify policy on which steroid nasal sprays are available fro prescription at Groote Schuur in the future.

Non-maleficence

The study will not result in any harm to the patients involved.

Process of obtaining informed consent and assent

Retrospective telephonic consent was obtained.

Stakeholder and reporting

The results of the study will be reported back to the Division of Otolaryngology at Groote Schuur Hospital in the format of a formal report.

References

1. Kalish L, Snidvongs K, Sivasubramaniam R, Cope D, Harvey RJ. Topical steroids for nasal polyps. Cochrane database Syst Rev 2012

2. Karlsson G, Rundcrantz H. A randomized trial in intranasal beclomethasone dipropionate after polypectomy. Rhinology 1982;20:144–8.

3. Virolainen E, Puhakka H. The effect of intranasal beclomethasone dipropionate on the recurrence of nasal polyps after ethmoidectomy. Rhinology 1980;18:9–18.

4. Stjärne P, Olsson P, Alenius M. Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg 2009;135(3):296–302.

5. Dingsør G, Kramer J, Olsholt R, Søderstrøm T. Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy. A randomized, double blind, parallel, placebo controlled study. Rhinology 1985;23:49–59.

6. Drettner B, Ebbesen A, Nilsson M. Prophylactive treatment with flunisolide after polypectomy. Rhinology 1982;20:149–58.

7. Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, Kennedy DW, et al. Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol. Head Neck Surg 2003;129(3):S1–32.

8. Williams AN, Woessner KM. The clinical effectiveness of aspirin desensitization in chronic rhinosinusitis. Curr Allergy Asthma Rep 2008;8(3):245–52.

9. McMains KC, Kountakis SE. Revision functional endoscopic sinus surgery: objective and subjective surgical outcomes. Am J Rhinol 2005;19(4):344–7.

10. Seybt MW, McMains KC, Kountakis SE. The prevalence and effect of asthma on adults with chronic rhinosinusitis. Ear Nose Throat J 2007;86(7):409–11.

11. McMains KC, Kountakis SE. Medical and surgical considerations in patients with Samter's triad. Am J Rhinol 2006;20(6):573–6.

12. Levine HL. Functional endoscopic sinus surgery: evaluation, surgery, and follow-up of 250 patients. Laryngoscope 1990;100:79–84.

13. Nishioka GJ, Cook PR, Davis WE, McKinsey JP. Functional endoscopic sinus surgery in patients with chronic sinusitis and asthma. Otolaryngol Head Neck Surg 1994;110:494–500.

14. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. Rhinology 2012;50(1):1–12.

15. Badia L, Lund V. Topical corticosteroids in nasal polyposis. Drugs 2001;61(5):573–8.

PART B: LITERATURE REVIEW

Literature Search Strategy

A literature search was undertaken of the PubMed, Medline and Cochrane databases for articles in journals that are listed on Index Medicus. The following keywords were used: “Corticosteroid nasal sprays”, “Corticosteroid comparison”, “Beclomethasone”, “Fluticasone” and “Mometasone”.

Summary Of Literature

Efficacy of corticosteroid nasal sprays

Topical corticosteroid nasal sprays are well-established first line therapy for chronic rhinosinusitis patients with or without nasal polyps[3–5]. They act by inhibiting the liberation of histamine, inhibiting the degranulation of basophils by reducing their cellular activity and circulating number[6].

The primary clinical benefits of topical nasal steroid preparations are produced by reducing nasal mucosal inflammation. They inhibit phospholipase in the arachidonic acid pathway. This effectively reduces the cell-mediated inflammatory response (basophils, mast cells, eosinophils and neutrophils), in addition to decreasing inflammatory mediator levels in nasal mucosa and nasal secretions. These actions inhibit both the early as well as late allergic responses[1].

Controlled studies have shown that topical steroids can delay the recurrence of polyps after surgery and with that postpone the need for revision surgery[2].

Comparing corticosteroid nasal sprays

Some feel there is no difference in the efficacy between the various preparations[2], but that is not the authors' opinion.

Beclomethasone dipropionate was introduced in 1970; fluticasone propionate and mometasone furoate were introduced later. Systemic absorption for these preparations is insignificant; less than or equal to 0.1% for fluticasone and mometasone and less than 10% for beclomethasone[6].

The efficacy of beclomethasone, fluticasone and mometasone nasal sprays in reducing polyp size and rhinitis symptoms has been shown in several randomised, placebo-controlled trials[3], but little work has been done to compare the various preparations to each other. The European position paper on rhinosinusitis and nasal polyps (2012) looked at 39 RCTs evaluating intranasal corticosteroids for CRSwNP. Of these 34 trials compared topical steroid against placebo; 8 trials compared low dose to high dose of topical steroid; 3 trials compared topical steroid to no intervention; and 3 trials compared steroid agents, fluticasone propionate and beclomethasone dipropionate[4].

Meta-analysis of the 34 RCTs comparing topical steroid against placebo analysed in EOPS 2012 showed significant benefit in the nasal steroid group for pooled

data analyses of symptoms, polyp size, polyp recurrence and nasal airflow compared to placebo[4].

Several placebo-controlled studies have shown the efficacy of corticosteroid sprays for reducing polyp size and CRS symptoms (obstruction, rhinorrhoea, post nasal drip and anosmia/hyposmia):

i. Beclomethasone: Bross-Soriano (2004), Holmberg (1997), Lund (1998), Mygrind (1975) and Karlsson (1982)[7–11].
ii. Fluticasone: Lund (1998), Olsson (2010), Aukema (2005), Bross-Soriano (2004), Holmberg (1997), Masterlerz (1997) and Rowe-Jones (2005)[7–9,12–15].
iii. Mometasone: Small (2005), Stjarne (2006, 2006b, 2009)[16–19].

When comparing the differences between the modern corticosteroids: fluticasone (15 trials), mometasone (6 trials) versus the first-generation corticosteroids: beclomethasone (7 trials), betamethasone (1 trial) and budesonide (9 trials); they found no significant difference between the two groups[4]. Only three trials compared the agents directly however.

Bross-Soriano (2004) compared beclomethasone, fluticasone and mometasone; concentrating on their effects in the intraocular pressure compartment rather than their efficacy at alleviating CRS symptoms. The author found discreet elevations in the beclomethasone and mometasone groups; however, these variations were within normal limits[6]. In a separate paper by the same author (2004),

beclomethasone, fluticasone were compared to control (saline lavage) post polypectomy. The findings showed 44% recurrence rate in the control group, compared to 26% in the beclomethasone group and 15% in fluticasone group[7].

Lund (1998) compared the efficacy beclomethasone and fluticasone to placebo in patients with severe polyposis listed for surgery. The author found a significantly decreased polyp score in the fluticasone treatment group; significantly increased nasal cavity volume as measured by acoustic rhinometry and decreased nasal obstruction in both the beclomethasone and fluticasone groups compared to placebo. The study showed some evidence that the fluticasone group responded more quickly and that the magnitude of the response was greater than in the beclomethasone group[9].

These findings were supplemented by Holmberg (1997) who also compared beclomethasone and fluticasone to placebo and found that both were effective at treating the symptoms of nasal polyps, with some evidence that fluticasone has a faster onset of action. No other statistically significant results were found between the two active compounds[8].

Efficacy at reducing polyp recurrence post-operatively

In 2004, Dijkstra's study showed no difference between fluticasone and placebo in controlling recurrent polyposis 1 year post FESS[20]. These findings are by far in the minority.

Besides shrinking intranasal polyps, corticosteroid nasal sprays also have an important role in preventing recurrence post-operatively. Karlsson (1982) found a

reduced polypectomy rate[11] and Virolainen (1980) a reduced symptomatic recurrence in patients using beclomethasone post-polypectomy.[21].

Dingsor (1985) and Drettner (1982) studied Flunisonide and found it significantly more effective than placebo in preventing polyp recurrence, treating chronic rhinosinusitis symptoms and reduced operation rate after polypectomy[22,23].

Hartwig (1998) found similar results with budesonide[24]. Thus, topical corticosteroid sprays are considered invaluable for long term maintenance post-operatively[3].

Stjatne (2009) found a significant longer time to relapse after FESS for patients using mometasone nasal spray compared to placebo[18].

The literature confirms that intranasal corticosteroids are the first line therapy for reducing polyp size; chronic rhinosinusitis related symptoms as well as reducing polyp recurrence rates post-operatively (and thereby reducing the number of polypectomies). All the steroid preparations included in our study have been found to be effective, but which is most efficacious?

References

1. Seiden AM, Tami T a., Pensak ML, Cotton RT, Gluckman JL. Otolaryngology: The Essentials. 2002.

2. Gleeson M. Scott-Brown's Otorhinolaryngology: Head and Neck Surgery 7Ed: 3 volume set. CRC Press; 2008.

3. Badia L, Lund V. Topical corticosteroids in nasal polyposis. Drugs 2001;61(5):573–8.

4. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. Rhinology 2012;50(1):1–12.

5. Kalish L, Snidvongs K, Sivasubramaniam R, Cope D, Harvey RJ. Topical steroids for nasal polyps. Cochrane database Syst Rev 2012;12(12):CD006549.

6. Bross-Soriano D, Hanenberg-Milver C, Schimelmitz-Idi J, Arrieta-Gomez JR, Del Toro RA, Bravo-Escobar G. Effects of three nasal topical steroids in the intraocular pressure compartment. Otolaryngol - Head Neck Surg 2004;130:187–91.

7. Bross-Soriano D, Arrieta-Gómez JR, Prado-Calleros H. Infections after endoscopic polypectomy using nasal steroids. Otolaryngol - Head Neck Surg 2004;130:319–22.

8. Holmberg K, Juliusson S, Balder B, Smith DL, Richards DH, Karlsson G. Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. 1997;78:270-276

9. Lund VJ, Flood J, Sykes a P, Richards DH. Effect of fluticasone in severe polyposis. Arch Otolaryngol Head Neck Surg 1998;124(5):513–8.

10. Mygind N, Pedersen CB, Prytz S, Sørensen H. Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. Clin Allergy 1975;5(2):159–64.

11. Karlsson G, Rundcrantz H. A randomized trial in intranasal beclomethasone dipropionate after polypectomy. Rhinology 1982;20:144–8.

12. Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. Rhinology 2005;43:2–10.

13. Olsson P, Ehnhage A, Nordin S, Stjärne P. Quality of life is improved by endoscopic surgery and fluticasone in nasal polyposis with asthma. Rhinology 2010;48:325–30.

14. Aukema A a C, Mulder PGH, Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. J Allergy Clin Immunol 2005;115(5):1017–23.

15. Mastalerz L, Milewski M, Duplaga M, Nizankowska E, Szczeklik a. Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. Allergy 1997;52(14):895–900.

16. Small CB, Hernandez J, Reyes A, Schenkel E, Damiano A, Stryszak P, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. J Allergy Clin Immunol 2005;116(6):1275–81.

17. Stjärne P, Mösges R, Jorissen M, Passàli D, Bellussi L, Staudinger H, et al. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. Arch Otolaryngol Head Neck Surg 2006;132(2):179–85.

18. Stjärne P, Olsson P, Alenius M. Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg 2009;135(3):296–302.

19. Stjärne P, Blomgren K, Cayé-Thomasen P, Salo S, Søderstrøm T. The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study. Acta Otolaryngol 2006;126(6):606–12.

20. Dijkstra MD, Ebbens F a, Poublon RML, Fokkens WJ. Fluticasone propionate aqueous nasal spray does not influence the recurrence rate of chronic rhinosinusitis and nasal polyps 1 year after functional endoscopic sinus surgery. Clin Exp Allergy 2004;34:1395–400.

21. Virolainen E, Puhakka H. The effect of intranasal beclomethasone dipropionate on the recurrence of nasal polyps after ethmoidectomy. Rhinology 1980;18:9–18.

22. Dingsør G, Kramer J, Olsholt R, Søderstrøm T. Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy. A randomized, double blind, parallel, placebo controlled study. Rhinology 1985;23:49–59.

23. Drettner B, Ebbesen A, Nilsson M. Prophylactive treatment with flunisolide after polypectomy. Rhinology 1982;20:149–58.

24. Hartwig S, Lindén M, Laurent C, Vargö a K, Lindqvist N. Budesonide nasal spray as prophylactic treatment after polypectomy (a double blind clinical trial). J Laryngol Otol 1988;102(February):148–51.

PART C: ARTICLE MANUSCRIPT

Comparing the efficacy of beclomethasone, fluticasone and mometasone sprays in a Samter's population

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Keywords:

Beclomethasone, fluticasone, mometasone, nasal polyps, nasal sprays

Summary

Statement of problem

Topical corticosteroids nasal sprays remain first line of treatment for patients with chronic rhinosinusitis (with or without nasal polyps). The main aim of treatment is to improve nasal symptoms by reducing or eliminating the nasal polyps[1] and preventing polyp recurrence post-operatively[2–6]. Our aims were to determine if the type of corticosteroid nasal spray used post operatively influences polyp recurrence rate and if there were any subsequent economic implications as we only have beclomethasone available for prescription in our state hospital.

Methods

Retrospective case note review of all Samter's patients who underwent fronto-spheno-ethmoidectomy by a single surgeon (2000 – 2014).

Results

58 patients were included in our study, divided into 3 study groups. When compared to patients using beclomethasone; patients using fluticasone had an 80% reduced risk of polyp recurrence and patients using mometasone a 90% reduced risk. This rose to 88% and 96% respectively when adjusted for age.

Conclusion

Fluticasone and mometasone are both statistically significantly more effective at reducing polyp recurrence than beclomethasone in our population group. Mometasone appeared more effective than fluticasone, but this difference was not statistically significant.

Introduction

Chronic rhinosinusitis (CRS) is defined as the presence of two or more symptoms, one of which should be either nasal blockage/obstruction/ congestion or nasal discharge (anterior/posterior nasal drip), with or without facial pain/pressure or reduction/loss of smell. These symptoms must be present for 12 weeks or more. It can be further classified as with polyps (CRSwNP) or without polyps (CRSsNP)[7].

Many theories as to the aetiology for nasal polyposis exist but the exact mechanism remains largely unknown. Regardless of aetiology, the increased presence of inflammatory mediators is prominent and consistent in nasal polyps[1]. There is an established connection with asthma and aspirin hypersensitivity (Samter's triad)[8]. The pathophysiology for this is only partially understood. The underlying respiratory disease is thought to be activated by an unknown mechanism[9]. In 1988, Szczeklik proposed that this trigger may be a chronic respiratory viral infection[10]. This results in an intense infiltration of mast cells and eosinophils into the entire respiratory mucosa[9]. Samter's patients are characterised by extensive nasal polyposis which responds well to functional endoscopic sinus surgery (FESS), but the polyps have a tendency to recur post-operatively[11–16].

Intranasal corticosteroid nasal sprays remain the well established first line of treatment for chronic rhinosinusitis patients with or without nasal polyps[1,7,17]. They act by inhibiting the liberation of histamine and inhibiting the degranulation of basophils by reducing their cellular activity and circulating numbers[18]. The efficacy of beclomethasone[2,19–22], fluticasone[19–21,23–26] and mometasone[4,27–29] nasal sprays in reducing polyp size and chronic rhinosinusitis symptoms (obstruction, rhinorrhoea, post nasal drip and anosmia/hyposmia) has been proven in several randomised, placebo-controlled trials[17]. We also know from the literature that they are effective in reducing polyp recurrence post-operatively[2–4]but little work has been done to

compare the various preparations to each other. This is especially pertinent in our clinical setting as Beclate™ (beclomethasone) is the only corticosteroid nasal spray available for prescription at our state funded hospital (Groote Schuur). This may appear to be a reasonable as it is the cheapest preparation to purchase, but we feel that once efficacy is factored in, this may not be the best economical choice.

Material and Methods

We retrospectively reviewed the case notes for all Samter's patients who had undergone fronto-spheno-ethmoidectomy for polyposis between 2004 and 2014. Patients were identified as Samter's if they had had a documented hypersensitivity reaction to Aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) and were asthmatic with nasal polyposis. All operations were by a single surgeon at either Groote Schuur (state) or Panorama (private) Hospitals in the Western Cape, South Africa. The data we collected included age at time or surgery, gender, number of previous FESS surgeries (by any surgeon), CAST (Cys-LT) result (if tested), date of fronto-spheno-ethmoidectomy and date of post-operative visit. At each post-operative visit the presence of nasal polyps on nasendoscopy, the nasal spray used, nasal spray compliance, whether the nasal spray used had changed since their previous visit and sense of smell were all noted. Patients with less than 6 months follow-up period post-operatively were excluded (unless polyps were noted to have recurred within 6 months). Patients that had changed nasal sprays between visits or were non-compliant were also excluded. Using the data collected; the time taken to notice polyp recurrence was calculated for each nasal spray and documented as a treatment failure. If no recurrence was noted on endoscopy, then the time since surgery was calculated and documented as a non-failure for that nasal spray. Stata12 was used for statistical analysis of Kaplan-Meier survival. Our institutional ethics review board approved this study.

Our aims were to compare the efficacy of various steroid nasal sprays at preventing polyp recurrence. To compare the efficacy of generic versus non-generic nasal sprays and to determine any cost implications.

Results

74 Samter's patients underwent fronto-spheno-ethmoidectomy between 2004 and 2014 at Groote Schuur and Panorama hospitals. Of these, 16 were excluded from the study due to non-compliance, changing of nasal sprays between follow-up visits or having less than 6 months follow-up period post-operatively (unless their polyps had already recurred). A total of 58 patients were included in the study. There were 34 female and 24 male patients with a mean age of 44 years. On average they had had 3 (1 – 11) previous FESS surgeries (all surgeons). Table 1 lists the different nasal sprays studied and the number of patients in each group. This data was then subdivided by active ingredient of the nasal spray, which left us with 3 study groups: beclomethasone, fluticasone and mometasone. The demographic data and follow-up data for each group are shown in Table 2.

ALL SPRAYs			TOT
Beclomethasone	Beclate	19	**19**
Fluticasone	Flixonase	6	**29**
	Flomist	12	
	Flonase	2	
	Avamys	9	
Mometasone	Nasonex	8	**10**
	Nexomist	1	
	Rinelon	1	

n=58

Table1: All nasal spray preparations; divided by active ingredient

SPRAYS	n	SEX		AGE (y)			FOLLOW-UP (m)		
		F	M	min	max	mean	min	max	mean
Beclomethasone	19	13	6	16	71	41	2.1	33.2	11.5
Fluticasone	29	15	14	20	76	47	4.6	63.5	19.3
Mometasone	10	6	4	31	53	41	6.9	55.4	27.6
Combined	**58**	**34**	**24**	**16**	**76**	**44**	**2.1**	**63.5**	**18.2**

Table 2: Summary of demographic data

Kaplan-Meier survival analysis comparing the time taken to notice polyp recurrence showed a significant difference between the nasal sprays. When compared to patients using beclomethasone nasal spray; the patients using fluticasone had an 80% reduced risk of developing polyp recurrence (p=0.000); and those on mometasone a 90% reduced risk (p=0.00) (Figure 1). When these figures are adjusted for age (which was found to be in independent risk factor for polyp recurrence) they rise to 88% reduced risk for fluticasone (p=0.000) and 95% reduced risk for mometasone (p=0.000) when compared to beclomethasone. The apparent advantage of mometasone over fluticasone was not statistically significant (p=0.121).

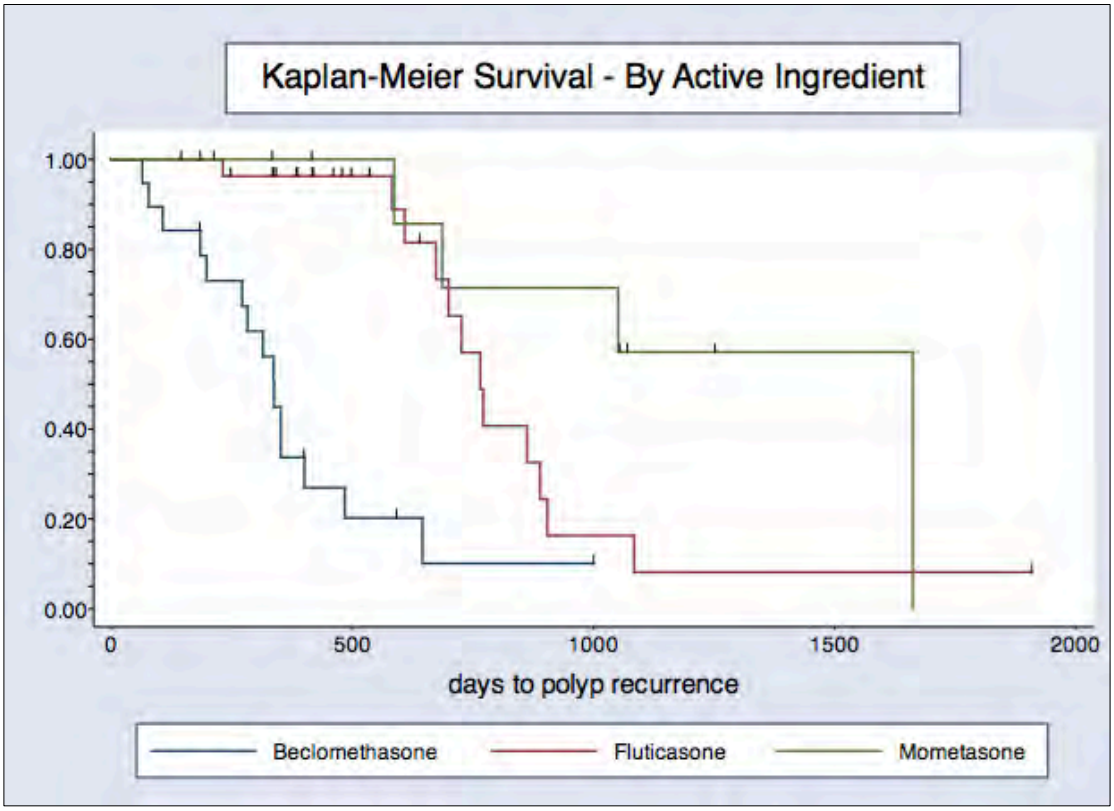

Figure 1: Kaplan-Meier survival analysis comparing time take to notice polyp recurrence for patients using beclomethasone, fluticasone and mometasone

Our study showed no statistical difference in efficacy when comparing fluticasone dipropionate original (Flixonase™), to the various fluticasone dipropionate generics (p=0.976) and the newest fluticasone preparation, fluticasone furoate (Avamys™)(p=0.412) (Figure 2).

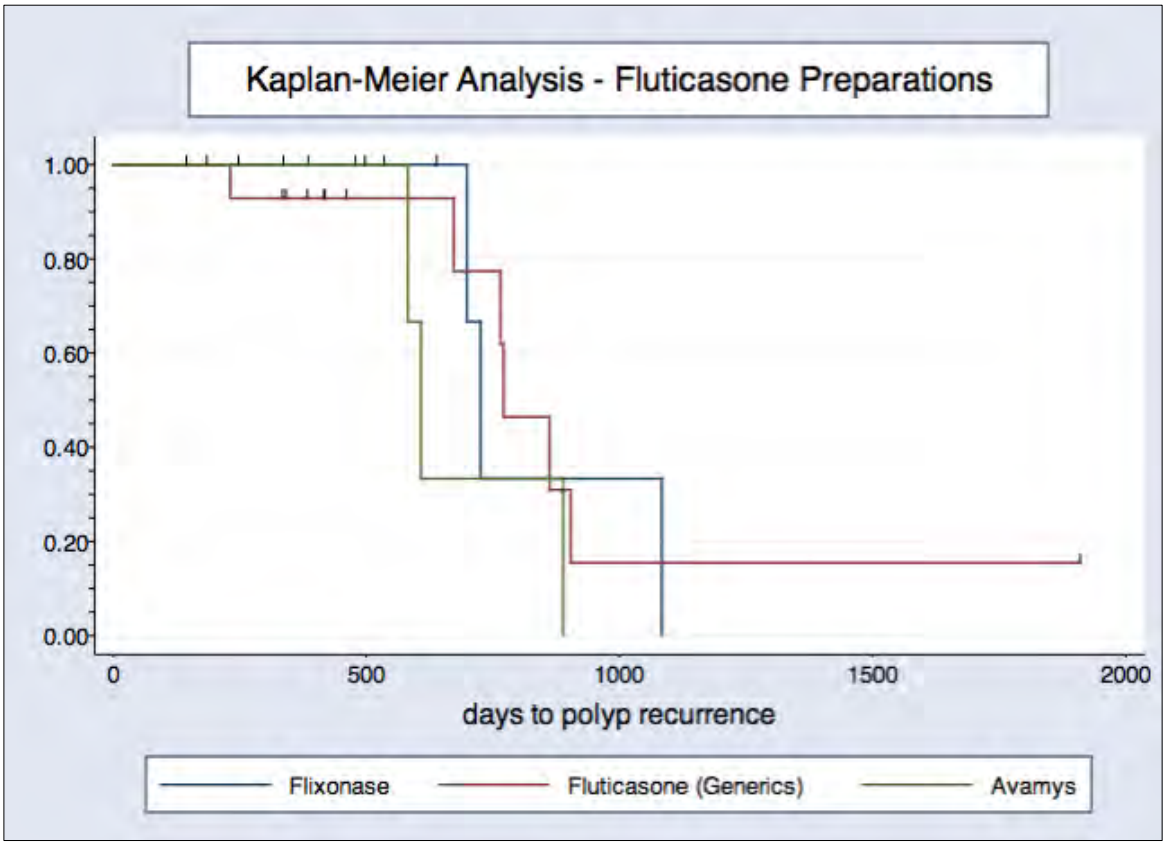

Figure 2: Kaplan-Meier survival analysis of comparing time taken to notice polyp recurrence for the various fluticasone preparations. No statistical difference is noted.

To ensure that our figures were not being skewed by socio-economic factors; we compared the rate of polyp recurrence in our state and private sector patients using fluticasone. Fluticasone was chosen, as it was the only spray with comparable numbers in both groups. We found no statistical difference between these 2 patients groups (p=0.522) (Figure 3).

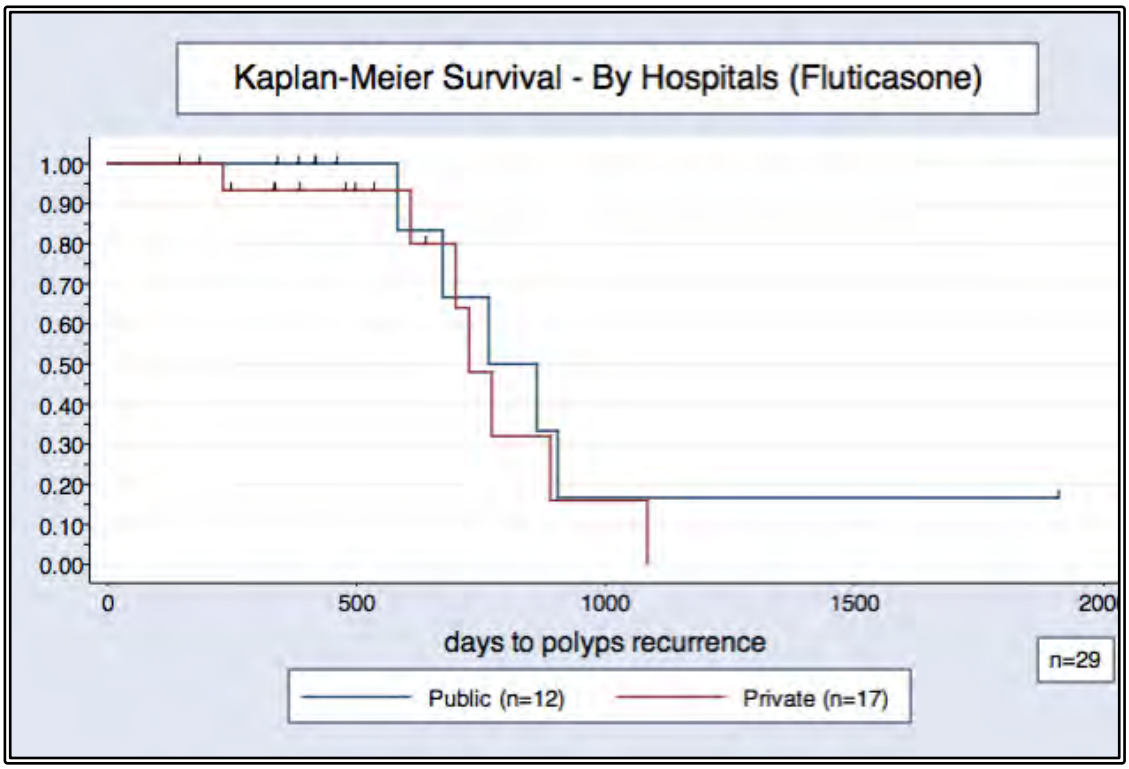

Figure 3: Kaplan-Meier survival analysis comparing the time taken to notice polyp recurrence in patients using fluticasone in the public and private sectors. No statistical difference is noted.

We also collected data on smell recovery post-operatively, but found no difference between the nasal sprays for this variable (p=0.6724).

14 of our patients, all of whom had previously documented hypersensitivity reactions to aspirin or other non-steroidal drugs, were sent for CAST (Cys-LT) testing. This is proposed as a safer alternative to aspirin challenge testing. Only 2 of these tests yielded a positive result, a sensitivity of only 14% for this test.

Discussion

Both fluticasone and mometasone nasal sprays were found to be significantly better than beclomethasone at reducing polyp recurrence post-operatively in our population group. Mometasone appeared more efficacious than fluticasone, but this was not statistically significant in our study.

We found no statistically significant difference in efficacy for the various fluticasone preparations; Flixonase™ (fluticasone propionate), fluticasone generics (fluticasone propionate) and Avamys™ (fluticasone furoate).

These findings are particularly significant in the setting of our public health sector, where only Beclate™ (beclomethasone) is available on state formulary for prescription. Table 3 lists the nasal sprays used in this study and compares the cost of using each preparation if used at maximal dose over a 28-day period. The monthly cost of using Beclate™ ($4,64) is approximately 30% less than the cost of using fluticasone ($6,81) or mometasone ($6,64). This is a significant difference in and on the face of it appears to justify the health department's decision. We know from previous studies, that corticosteroid nasal spray are effective at reducing polyp recurrence as well as re-operation rate[2–6]. Thus, it is only when the cost of FESS surgery is considered that an accurate cost assessment can be made. Even in the state sector, the cost of FESS surgery is $520 (R6000). If this cost is divided by the difference in cost between beclomethasone and mometasone ($520/($6.64-$4,64)), this equates to using the "more expensive" mometasone for 260 months or 21 years. We did not have

enough data in our study to comment on the respective re-operation rates for each nasal spray, but given the significant difference we were able to demonstrate in reduced polyp recurrence, it is not unreasonable to infer that this may result in fewer operations for patients using fluticasone or mometasone. If this resulted in just one fewer operation over a 21-year period for the patients using fluticasone or mometasone compared to patients using beclomethasone, then what initially appears to be the more expensive option actually becomes the more economical option long term. And that is before immeasurables such as increased risk of complications for revision surgery[30,31] and work absence, are factored in.

	METERED DOSE (mcg/spray)	DOSES (per bottle)	DOSES per 28 DAYS (@ max dose)	COST (per bottle)	COST (per spray)	COST per 28 DAYS (ZAR)	**COST per 28 DAYS (USD)**
BECLAMETHASONE							
BECLATE	50	150	112	71,50	0,48	53,39	**4,64**
FLUTICASONE							
FLOMIST/FLONASE	50	100	112	69,89	0,70	78,28	**6,81**
AVAMYS	27,5	120	56	177,40	1,48	82,79	**7,20**
FLIXONASE	50	120	112	214,00	1,78	199,73	**17,37**
MOMETASONE							
NEXOMIST	50	140	56	191,00	1,36	76,40	**6,64**
RINELON	50	140	56	198,95	1,42	79,58	**6,92**
NASONEX	50	120	56	227,28	1,89	106,06	**9,22**

Table 3: Cost comparison for usage of steroid nasal sprays in this study. Cost is calculated if used at maximum prescribed dosage per 28 days.

All the patients in our study had previously documented hypersensitivity reactions to aspirin or other NSAIDs. Most had bronchospasm requiring admission to hospital, and few required ICU admission.

Although aspirin challenge testing (oral or inhalational) is considered the gold standard for the diagnosis of aspirin hypersensitivity, this can be associated with severe adverse reactions and is not widely available in our setting (nor is desensitisation). The cellular allergen stimulation test assay (CAST) was introduced in the early 1990's as quick, safer alternative to aspirin challenge testing. Evaluation of this test has revealed variable results. Earlier studies showed some promise with good sensitivity (80 – 100%) and specificity (70-100%) results[32–34], but more recent studies confirm our findings with sensitivity below 30%[35–37]. Given these findings, we could find no role for this test in the diagnosis of aspirin hypersensitivity.

Conclusions

We were able to demonstrate a significant advantage in efficacy at reducing polyp recurrence for the newer generation corticosteroid nasal sprays (fluticasone and mometasone) over beclomethasone in our Samter's population group. Given this overwhelming advantage, we feel confident that this should translate to reduced operation rates and therefore prove to be more cost effective in the long term. We hope to be able to show this by continuing with this research prospectively and in doing so, change our hospital's prescribing policy.

Acknowledgements

No competing interests to declare. This research was not sponsored by any pharmaceuticals.

References

1. Kalish L, Snidvongs K, Sivasubramaniam R, Cope D, Harvey RJ. Topical steroids for nasal polyps. Cochrane database Syst Rev 2012;12(12):CD006549.

2. Karlsson G, Rundcrantz H. A randomized trial in intranasal beclomethasone dipropionate after polypectomy. Rhinology 1982;20:144–8.

3. Virolainen E, Puhakka H. The effect of intranasal beclomethasone dipropionate on the recurrence of nasal polyps after ethmoidectomy. Rhinology 1980;18:9–18.

4. Stjärne P, Olsson P, Alenius M. Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg 2009;135(3):296–302.

5. Dingsør G, Kramer J, Olsholt R, Søderstrøm T. Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy. A randomized, double blind, parallel, placebo controlled study. Rhinology 1985;23:49–59.

6. Drettner B, Ebbesen A, Nilsson M. Prophylactive treatment with flunisolide after polypectomy. Rhinology 1982;20:149–58.

7. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. Rhinology 2012;50(1):1–12.

8. Slavin R. Nasal polyps and sinusitis. Clin Allegy Immunol 2002;16:295–309.

9. Laidlaw TM, Boyce JA. Pathogenesis of Aspirin-Exacerbated Respiratory Disease and Reactions. Immunol. Allergy Clin. North Am.2013;33:195–210.

10. Szczeklik a. Aspirin-induced asthma as a viral disease. Clin Allergy 1988;18:15–20.

11. Friedman WH, Katsantonis GP, Slavin RG, Kannel P, Linford P. Sphenoethmoidectomy: its role in the asthmatic patient. Otolaryngol Head Neck Surg 90:171–7.

12. Levine HL. Functional endoscopic sinus surgery: evaluation, surgery, and follow-up of 250 patients. Laryngoscope 1990;100:79–84.

13. Nishioka GJ, Cook PR, Davis WE, McKinsey JP. Functional endoscopic sinus surgery in patients with chronic sinusitis and asthma. Otolaryngol - Head Neck Surg 1994;110:494–500.

14. Seybt MW, McMains KC, Kountakis SE. The prevalence and effect of asthma on adults with chronic rhinosinusitis. Ear Nose Throat J 2007;86(7):409–11.

15. McMains KC, Kountakis SE. Revision functional endoscopic sinus surgery: objective and subjective surgical outcomes. Am J Rhinol 2005;19(4):344–7.

16. McMains KC, Kountakis SE. Medical and surgical considerations in patients with Samter's triad. Am J Rhinol 2006;20(6):573–6.

17. Badia L, Lund V. Topical corticosteroids in nasal polyposis. Drugs 2001;61(5):573–8.

18. Bross-Soriano D, Hanenberg-Milver C, Schimelmitz-Idi J, Arrieta-Gomez JR, Del Toro RA, Bravo-Escobar G. Effects of three nasal topical steroids in the intraocular pressure compartment. Otolaryngol - Head Neck Surg 2004;130:187–91.

19. Bross-Soriano D, Arrieta-Gómez JR, Prado-Calleros H. Infections after endoscopic polypectomy using nasal steroids. Otolaryngol - Head Neck Surg 2004;130:319–22.

20. Holmberg K, Juliusson S, Balder B, Smith DL, Richards DH, Karlsson G. Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. 1997;78:270-276

21. Lund VJ, Flood J, Sykes a P, Richards DH. Effect of fluticasone in severe polyposis. Arch Otolaryngol Head Neck Surg 1998;124(5):513–8.

22. Mygind N, Pedersen CB, Prytz S, Sørensen H. Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. Clin Allergy 1975;5(2):159–64.

23. Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. Rhinology 2005;43:2–10.

24. Olsson P, Ehnhage A, Nordin S, Stjärne P. Quality of life is improved by endoscopic surgery and fluticasone in nasal polyposis with asthma. Rhinology 2010;48:325–30.

25. Aukema A a C, Mulder PGH, Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. J Allergy Clin Immunol 2005;115(5):1017–23.

26. Mastalerz L, Milewski M, Duplaga M, Nizankowska E, Szczeklik a. Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. Allergy 1997;52(14):895–900.

27. Small CB, Hernandez J, Reyes A, Schenkel E, Damiano A, Stryszak P, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. J Allergy Clin Immunol 2005;116(6):1275–81.

28. Stjärne P, Blomgren K, Cayé-Thomasen P, Salo S, Søderstrøm T. The efficacy and safety of once-daily mometasone furoate nasal spray in nasal

polyposis: a randomized, double-blind, placebo-controlled study. Acta Otolaryngol 2006;126(6):606–12.

29. Stjärne P, Mösges R, Jorissen M, Passàli D, Bellussi L, Staudinger H, et al. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. Arch Otolaryngol Head Neck Surg 2006;132(2):179–85.

30. Moses RL, Cornetta a, Atkins JP, Roth M, Rosen MR, Keane WM. Revision endoscopic sinus surgery: the Thomas Jefferson University experience. Ear Nose Throat J 1998;77:190, 193–5, 199–202.

31. Krings JG, Kallogjeri D, Wineland A, Nepple KG, Piccirillo JF, Getz AE. Complications of primary and revision functional endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope 2014;124(April):838–45.

32. Czech W, Schopf E, Kapp A. Release of sulfidoleukotrienes in vitro: Its relevance in the diagnosis of pseudoallergy to acetylsalicylic acid. Inflamm Res 1995;44:291–5.

33. Kubota Y, Imayama S, Toshitani A, Miyahara H, Tanahashi T, Uemura Y, et al. Sulfidoleukotriene release test (CAST) in hypersensitivity to nonsteroidal anti-inflammatory drugs. Int Arch Allergy Immunol 1997;114:361–6.

34. Wedi B, Kapp A. Aspirin induced adverse skin reactions: new pathophysiological aspects. Thorax 2000;S70-S71.

35. Bavbek S, Dursun a B, Birben E, Kalayci O, Misirligil Z. Cellular allergen stimulation test with acetylsalicylic acid-lysine is not a useful test to discriminate between asthmatic patients with and without acetylsalicylic acid sensitivity. Int Arch Allergy Immunol 2009;149(1):58–64.

36. Lebel B, Messaad D, Kvedariene V, Rongier M, Bousquet J, Demoly P. Cysteinyl-leukotriene release test (CAST) in the diagnosis of immediate drug reactions. Allergy 2001;56:688–92.

37. Sanz ML, Gamboa P, De Weck AL. A new combined test with flowcytometric basophil activation and determination of sulfidoleukotrienes is useful for in vitro diagnosis of hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs. Int Arch Allergy Immunol 2005;136:58–72.

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Tables and Figures

Table 1.

ALL SPRAYs			TOT
Beclomethasone	Beclate	19	**19**
Fluticasone	Flixonase	6	**29**
	Flomist	12	
	Flonase	2	
	Avamys	9	
Mometasone	Nasonex	8	**10**
	Nexomist	1	
	Rinelon	1	

n=58

Table 2.

SPRAYS	n	SEX		AGE (y)			FOLLOW-UP (m)		
		F	M	min	max	mean	min	max	mean
Beclomethasone	19	13	6	16	71	41	2.1	33.2	11.5
Fluticasone	29	15	14	20	76	47	4.6	63.5	19.3
Mometasone	10	6	4	31	53	41	6.9	55.4	27.6
Combined	**58**	**34**	**24**	**16**	**76**	**44**	**2.1**	**63.5**	**18.2**

Table 3.

	METERED DOSE (mcg/spray)	DOSES (per bottle)	DOSES per 28 DAYS (@ max dose)	COST (per bottle)	COST (per spray)	COST per 28 DAYS (ZAR)	**COST per 28 DAYS (USD)**
BECLAMETHASONE							
BECLATE	50	150	112	71,50	0,48	53,39	**4,64**
FLUTICASONE							
FLOMIST/FLONASE	50	100	112	69,89	0,70	78,28	**6,81**
AVAMYS	27,5	120	56	177,40	1,48	82,79	**7,20**
FLIXONASE	50	120	112	214,00	1,78	199,73	**17,37**
MOMETASONE							
NEXOMIST	50	140	56	191,00	1,36	76,40	**6,64**
RINELON	50	140	56	198,95	1,42	79,58	**6,92**
NASONEX	50	120	56	227,28	1,89	106,06	**9,22**

Figure 1.

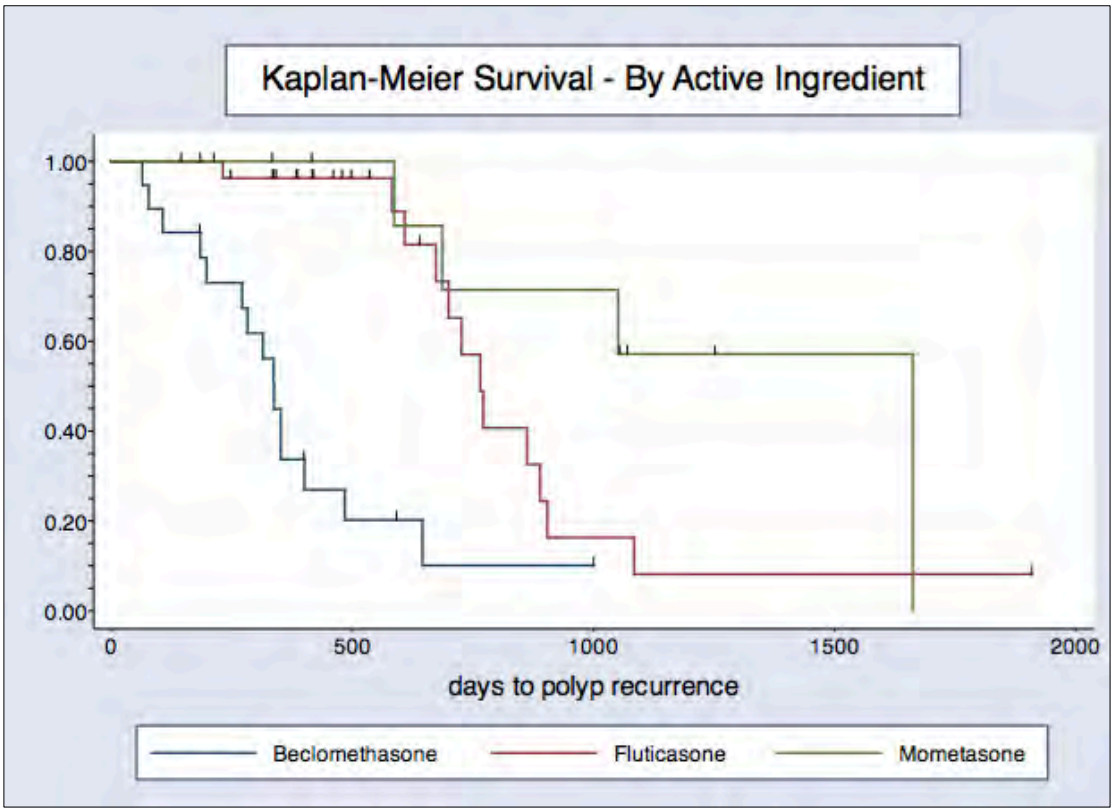


Figure 2.

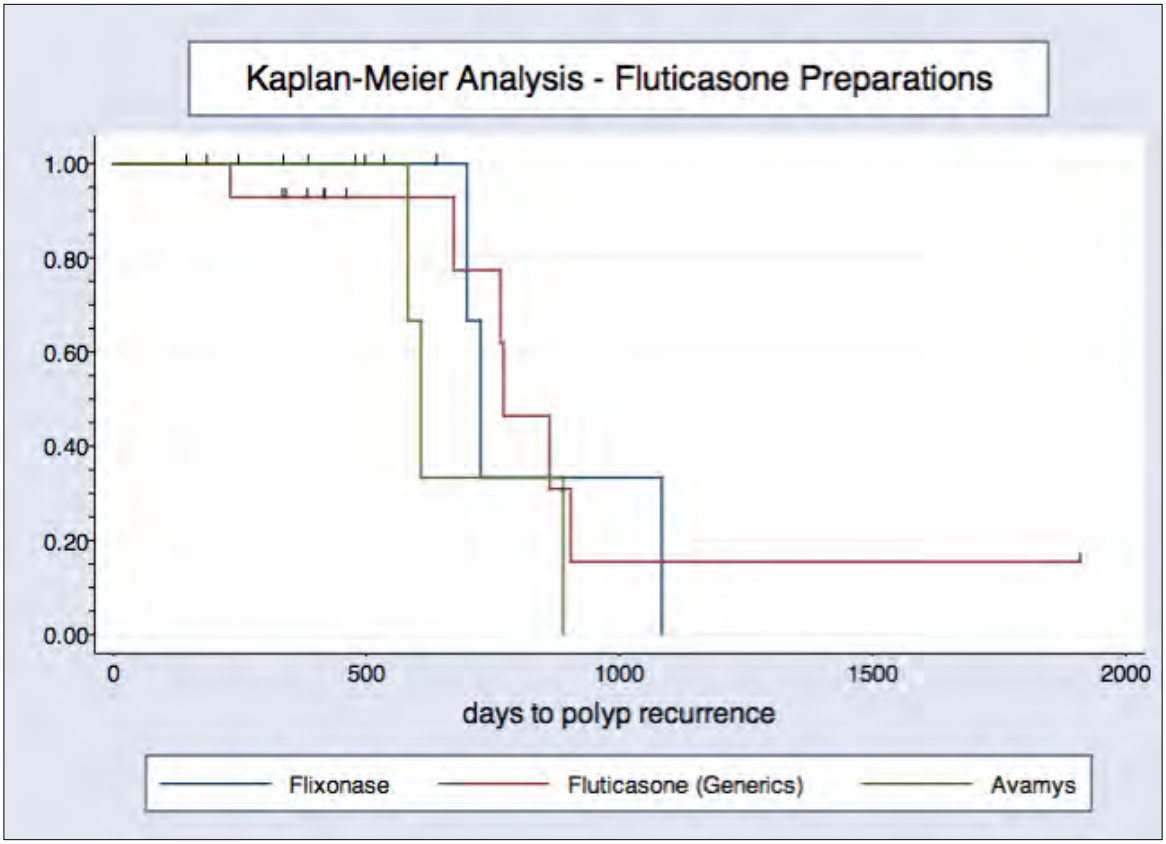
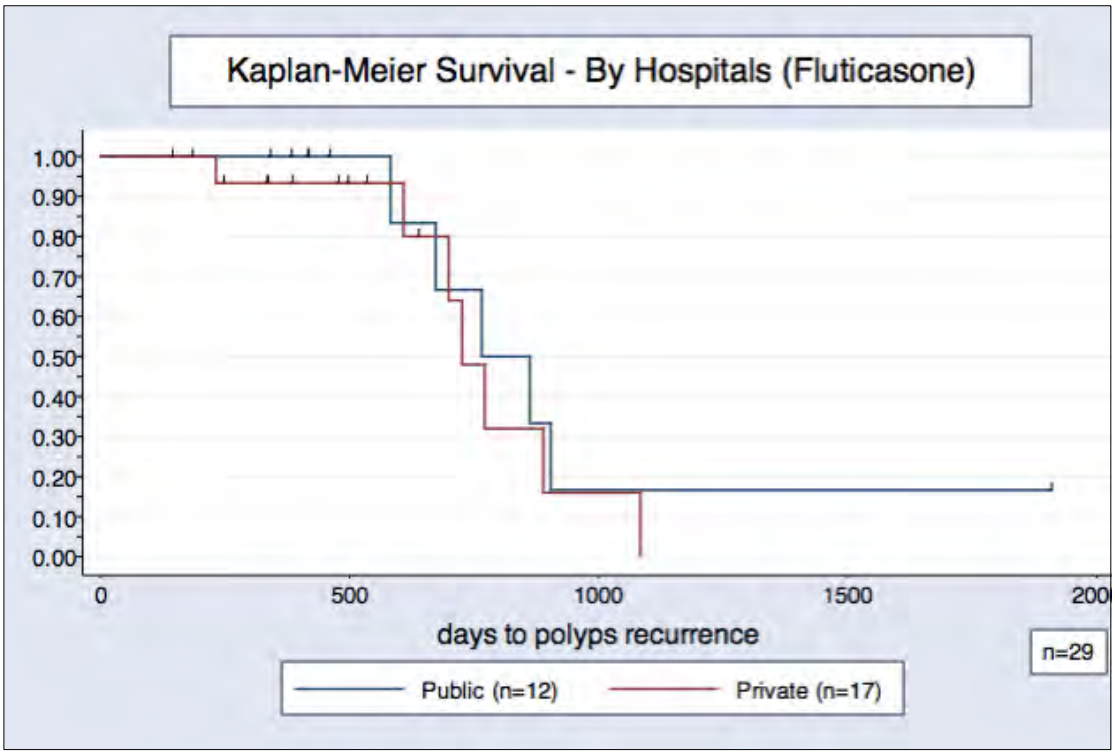


Figure 3.


Kaplan-Meier Survival - By Hospitals (Fluticasone)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
500
1000
1500
200
days to polyps recurrence
n=29
Public (n=12)
Private (n=17)

Legends for Illustrations

Figure 1: *Kaplan-Meier survival analysis comparing time take to notice polyp recurrence for patients using beclomethasone, fluticasone and mometasone*

Figure 2: *Kaplan-Meier survival analysis of comparing time taken to notice polyp recurrence for the various fluticasone preparations. No statistical difference is noted.*

Figure 3: *Kaplan-Meier survival analysis comparing the time taken to notice polyp recurrence in patients using fluticasone in the public and private sectors. No statistical difference is noted.*

Legends for Tables

Table1: *All nasal spray preparations; divided by active ingredient*

Table 2*: Summary of demographic data*

Table 3: *Cost comparison for usage of steroid nasal sprays in this study. Cost is calculated if used at maximum prescribed dosage per 28 days.*

PART D: APPENDICES

Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

24 December 2014

HREC REF: 903/2014

A/Prof D Lubbe
Otorhinolaryngology
ENT
H-53 OMB

Dear A/Prof Lubbe

PROJECT TITLE: COMPARING THE EFFICACY OF VARIOUS CORTICOSTEROID NASAL SPRAYS IN SAMTER'S POPULATION GROUP (MMEd candidate-Dr P Monteiro)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th December 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr P Monteiro will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

Departmental Research Committee Approval

UNIVERSITY OF CAPE TOWN

Department of Surgery

Departmental Research Committee
Professor Anwar Suleman Mall
J-45 Room Old Main Building, Groote Schuur Hospital,
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Tel (021) 406 6168/6232/6227 Fax (021) 448 6461
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1st December 2014

Dr P Monteiro
Department of Surgery
Division of Otolaryngology
Groote Schuur Hospital
University of Cape Town

Dear Dr Monteiro,

RE: PROJECT 2014/116

PROJECT TITLE: Comparing the efficacy of various corticosteroid nasal sprays in Samter's patients

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

Signed by candidate

PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE

Data Capture Sheet

number	sex	dob	hospital	asthma	number FESS	aspirin sensitivity	CAST	lys-aspirin	lys-a interpretation	surgery date	follow up	spray used	polyps present	days to recurrence	days disease free	smell recovery
1	f	11/12/1946	GSH	y	4	y	y	41	neg	18/10/2011	16/01/2013	flomist	n	no recurrence	456	n
2	f	07/12/1950	GSH	y	4	y	n			13/11/2012	15/05/2013	beclate	n	no recurrence	183	u
3	f	12/08/1948	GSH	y	3	y	n			7/02/2012	27/03/2013	flomist	n	no recurrence	414	n
4	m	1/09/1955	GSH	y	1	y	y	43	neg	27/09/2011	26/10/2012	beclate	n	no recurrence	395	n
5	m	20/05/1956	GSH	y	8	y	de	de	de	17/08/2010	31/08/2011	flomist	n	no recurrence	379	n
6	f	19/02/1949	GSH	y	1	y	n			31/05/2011	2/05/2012	flomist	n	no recurrence	337	n
7	f	7/02/1962	GSH	y	2	y	n			15/03/2011	26/10/2012	beclate	n	no recurrence	591	y
8	f	20/02/1992	PH	y	1	y	n			24/09/2012	11/02/2013	avamys	n	no recurrence	140	y
9	f	20/11/1962	PH	y	2	y	y	75	pos	21/03/2012	15/10/2012	nasonex	n	no recurrence	208	y
10	f	3/09/1977	PH	y	4	y	n			22/05/2009	25/10/2012	rinelon	n	no recurrence	1252	n
11	m	23/05/1966	PH	y	2	y	n			13/05/2011	25/10/2012	flixonase	n	no recurrence	531	y
12	f	29/08/1933	PH	y	2	y	n			6/08/2010	2/05/2012	flixonase	n	no recurrence	635	y
13	f	31/05/1959	PH	y	3	y	y	0	neg	7/05/2009	26/03/2012	nasonex	n	no recurrence	1054	y
14	f	26/11/1964	PH	y	8	y	n			30/11/2011	25/10/2012	flonase	n	no recurrence	330	y
15	m	9/10/1960	PH	y	2	y	n			15/08/2012	15/04/2013	avamys	n	no recurrence	243	y
16	f	3/08/1955	PH	y	1	y	n			15/04/2011	12/03/2012	avamys	n	no recurrence	332	y
17	f	11/12/1946	GSH	y	4	y	y	41	neg	5/08/2008	26/01/2011	flomist	y	904		n
18	f	11/12/1946	GSH	y	4	y	de	de	de	11/07/2006	16/04/2008	beclate	y	645		n
19	m	20/05/1956	GSH	y	9	y	y	0	neg	3/06/2008	7/04/2010	flomist	y	673		n
20	m	20/05/1956	GSH	y	9	y	y	0	neg	17/08/2010	31/08/2011	flomist	n	no recurrence	379	n
21	f	18/09/1964	GSH	y	1	y	n			18/01/2011	4/05/2011	beclate	y	106		n
22	m	19/11/1958	GSH	y	1	y	n			29/06/2010	31/05/2011	beclate	y	336		y
23	f	01/12/1949	GSH	y	11	y	y	0	neg	3/06/2008	21/08/2013	flomist	n	no recurrence	1905	y
24	f	15/10/1938	GSH	y	4	y	n			24/08/2010	16/05/2013	beclate	n	no recurrence	996	n
25	f	24/10/1947	GSH	y	2	y	y	27	neg	11/05/2011	27/07/2011	beclate	y	77		y
26	f	24/09/1962	GSH	y	2	y	n			31/05/2011	26/09/2012	beclate	y	484		n
27	m	06/10/1992	GSH	y	3	y	n			11/04/2009	18/01/2010	beclate	y	282		n
28	m	06/10/1992	GSH	y	3	y	n			13/07/2010	15/09/2010	beclate	y	64		n
29	m	06/10/1992	GSH	y	3	y	n			16/10/2012	18/09/2013	beclate	y	337		n
30	m	25/05/1979	GSH	y	3	y	y	0	neg	13/05/2011	8/02/2012	beclate	y	271		y
31	m	12/12/1962	GSH	y	4	y	n			1/06/2011	3/01/2013	avamys	y	582		n
32	f	01/01/1972	GSH	y	1	y	y	45	neg	29/03/2011	29/09/2011	beclate	y	184		n
33	f	11/04/1952	GSH	y	3	y	n			7/10/2008	16/02/2011	flomist	y	862		y
34	f	21/10/1982	GSH	y	2	y	n			23/10/2012	8/05/2013	beclate	y	197		y
35	f	21/10/1982	GSH	y	2	y	n			19/04/2011	4/04/2012	beclate	y	351		n
36	f	14/03/1974	GSH	y	1	y	n			17/07/2012	21/08/2013	beclate	y	400		n
37	f	10/04/1974	GSH	y	2	y	n			2/02/2010	13/12/2010	beclate	y	314		n
38	f	12/01/1979	GSH	y	3	y	de	de	de	19/06/2012	5/08/2013	flomist	n	no recurrence	412	n
39	f	12/01/1979	GSH	y	3	y	de	de	de	16/10/2007	19/11/2009	flomist	y	765		n
40	f	12/01/1979	GSH	y	3	y	de	de	de	1/08/2006	18/07/2007	beclate	y	351		n
41	f	14/06/1963	PH	y	2	y	y	?	neg	27/07/2012	12/08/2013	avamys	n	no recurrence	381	y
42	m	8/09/1943	PH	y	4	y	y	?	pos	3/08/2011	19/11/2012	avamys	n	no recurrence	474	y
43	m	7/05/1969	PH	y	5	y	n			25/02/2011	25/10/2012	avamys	y	608		n
44	m	18/12/1975	PH	y	3	y	n			3/11/2010	11/06/2012	nexomist	y	586		y
45	m	18/12/1975	PH	y	3	y	n			8/12/2008	25/10/2010	nasonex	y	686		n
46	m	13/06/1983	PH	y	4	y	y	0	neg	6/12/2010	25/07/2011	flomist	y	231		n
47	f	10/01/1959	PH	y	3	y	n			20/04/2012	15/03/2013	nasonex	n	no recurrence	329	n
48	f	28/11/1957	PH	y	1	y	n			4/11/2011	3/10/2013	flixonase	y	699		n
49	f	16/08/1978	PH	y	1	y	n			3/04/2013	30/09/2013	avamys	n	no recurrence	180	y
50	f	1/02/1962	PH	y	2	y	n			25/08/2010	11/07/2013	nasonex	y	1051		u
51	m	17/06/1966	PH	y	2	y	n			19/06/2009	24/05/2012	nasonex	n	no recurrence	1070	y
52	m	30/04/1980	PH	y	2	y	n			15/08/2012	30/09/2013	nasonex	n	no recurrence	411	u
53	m	30/05/1968	PH	y	4	y	n			2/12/2011	8/04/2013	flixonase	n	no recurrence	493	y
54	m	12/11/1974	PH	y	?	y	n			16/11/2011	11/11/2013	flixonase	y	726		u
55	m	26/10/1970	PH	y	5	y	n			21/05/2010	9/05/2013	flixonase	y	1084		n
56	m	12/09/1969	PH	y	2	y	n			24/11/2010	1/05/2013	avamys	y	889		y
57	f	8/01/1967	PH	y	3	y	n			1/02/2008	20/08/2012	nasonex	y	1662		n
58	m	7/11/1976	PH	y	3	y	n			29/06/2011	8/08/2013	flonase	y	771		y

STATA

Nasal sprays by active ingredient:

spraynew	person-time	failures	rate	[95% Conf.	Interval]
Beclome~e	6564.0000	15	2.2852	1.3777	3.7905
Flutica~e	16815.0000	12	0.7136	0.4053	1.2566
Mometas~e	8309.0000	4	0.4814	0.1807	1.2827
total	31688.0001	31	0.9783	0.6880	1.3911

Nasal sprays: Age distribution:

-> spraynew = Beclomethasone

variable	N	min	max	mean	sd	p50	iqr
ageyrs	19	16	71	41.31579	16.40817	39	28

-> spraynew = Fluticasone

variable	N	min	max	mean	sd	p50	iqr
ageyrs	29	20	76	47.96552	13.24355	49	17

-> spraynew = Mometasone

variable	N	min	max	mean	sd	p50	iqr
ageyrs	10	31	53	41.2	8.403703	42	17

Nasal sprays: Follow-up:

-> spraynew = Beclomethasone

variable	N	min	max	mean	sd	p50	iqr
fupdays	19	64	996	345.4737	222.5804	336	216

-> spraynew = Fluticasone

variable	N	min	max	mean	sd	p50	iqr
fupdays	29	140	1905	579.8276	348.1099	493	347

-> spraynew = Mometasone

variable	N	min	max	mean	sd	p50	iqr
fupdays	10	208	1662	830.9	461.9566	868.5	659

Log-rank test for equality of survivor functions:

spraynew	Events observed	Events expected
Beclomethasone	15	4.96
Fluticasone	12	16.32
Mometasone	4	9.72
Total	31	31.00

chi2(2) = 27.38
Pr>chi2 = 0.0000

Survival analysis: Crude hazard ratio: Polyp recurrence rate
(spraycat1=beclomethasone, spraycat2=fluticasone, spraycat3=mometasone)

```
.  *** Crude Hazard Ratio  ******
.
.   xi: stcox i.spraycat
i.spraycat        _Ispraycat_1-3      (naturally coded; _Ispraycat_1 omitted)

         failure _d:  recur
   analysis time _t:  survivaltime
                 id:  id

Iteration 0:   log likelihood = -96.462181
Iteration 1:   log likelihood =  -87.56107
Iteration 2:   log likelihood = -85.622729
Iteration 3:   log likelihood = -85.582459
Iteration 4:   log likelihood = -85.582455
Refining estimates:
Iteration 0:   log likelihood = -85.582455

Cox regression -- Breslow method for ties

No. of subjects =           58                     Number of obs    =        58
No. of failures =           31
Time at risk    =        32073
                                                   LR chi2(2)       =     21.76
Log likelihood  =   -85.582455                     Prob > chi2      =    0.0000
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Ispraycat_2	.188241	.0784244	-4.01	0.000	.0831935	.4259308
_Ispraycat_3	.0933182	.0576794	-3.84	0.000	.0277872	.3133926

Survival analysis: Age adjusted hazard ratio: Polyp recurrence rate
(spraycat1=beclomethasone, spraycat2=fluticasone, spraycat3=mometasone)

```
.  ** Adjusted Hazard Ratio *****
.
.    xi: stcox i.spraycat ageyrs
i.spraycat        _Ispraycat_1-3      (naturally coded; _Ispraycat_1 omitted)

         failure _d:  recur
   analysis time _t:  survivaltime
                 id:  id

Iteration 0:   log likelihood = -96.462181
Iteration 1:   log likelihood = -77.241852
Iteration 2:   log likelihood = -76.910239
Iteration 3:   log likelihood = -76.907694
Iteration 4:   log likelihood = -76.907694
Refining estimates:
Iteration 0:   log likelihood = -76.907694

Cox regression -- Breslow method for ties

No. of subjects =           58                     Number of obs    =        58
No. of failures =           31
Time at risk    =        32073
                                                   LR chi2(3)       =     39.11
Log likelihood  =   -76.907694                     Prob > chi2      =    0.0000
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Ispraycat_2	.1133354	.059974	-4.11	0.000	.0401729	.3197409
_Ispraycat_3	.0367538	.0268661	-4.52	0.000	.0087719	.1539958
ageyrs	.9415158	.0145691	-3.89	0.000	.9133897	.9705081

Log rank test for equality of survivors: Fluticasone v Mometasone: Polyp recurrence

spraynew	Events observed	Events expected
Fluticasone	12	8.92
Mometasone	4	7.08
Total	16	16.00

chi2(1) = 2.55
Pr>chi2 = 0.1106

Survival analysis: Crude hazard ratio: Fluticasone v Mometasone: Polyp recurrence rate
(spraycat1=fluticasone, spraycat2=mometasone)

```
. xi: stcox i.spraynew
i.spraynew        _Ispraynew_2-3      (naturally coded; _Ispraynew_2 omitted)

         failure _d:  recur
   analysis time _t:  survivaltime
                 id:  id

Iteration 0:   log likelihood = -38.586112
Iteration 1:   log likelihood = -37.247876
Iteration 2:   log likelihood = -37.235983
Iteration 3:   log likelihood = -37.235978
Refining estimates:
Iteration 0:   log likelihood = -37.235978

Cox regression -- no ties

No. of subjects =           39                 Number of obs    =        39
No. of failures =           16
Time at risk    =        25124
                                               LR chi2(1)       =      2.70
Log likelihood  =   -37.235978                 Prob > chi2      =    0.1003
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Ispraynew_3	.4000967	.2366616	-1.55	0.121	.1255075	1.27544

Log rank test for equality of survivor functions: Fluticasone preparations

spraynew3	Events observed	Events expected
2	3	3.34
3	6	6.91
5	3	1.75
Total	12	12.00

chi2(2) = 1.10
Pr>chi2 = 0.5768

Survival analysis: Crude hazard ratio: Polyp recurrence rate (Fluticasone preparations)
(spraycat1=Flixonase, spraycat2=fluticasone generics, spraycat3=Avamys)

```
. xi: stcox i.spraynew3
i.spraynew3       _Ispraynew3_2-5     (naturally coded; _Ispraynew3_2 omitted)

        failure _d:  recur
  analysis time _t:  survivaltime
                id:  id

Iteration 0:   log likelihood = -23.450105
Iteration 1:   log likelihood = -23.000472
Iteration 2:   log likelihood = -22.973416
Iteration 3:   log likelihood = -22.973397
Refining estimates:
Iteration 0:   log likelihood = -22.973397

Cox regression -- no ties

No. of subjects =           29                 Number of obs    =        29
No. of failures =           12
Time at risk    =        16815
                                               LR chi2(2)       =      0.95
Log likelihood  =   -22.973397                 Prob > chi2      =    0.6208
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Ispraynew3_3	.9786663	.7034084	-0.03	0.976	.2392437	4.003398
_Ispraynew3_5	2.023977	1.738077	0.82	0.412	.3760468	10.89355

Log rank test for equality of survivor functions: Hospitals (Fluticasone, polyp recurrence)

hospital	Events observed	Events expected
GSH	5	6.11
Panorama	7	5.89
Total	12	12.00

chi2(1) = 0.42
Pr>chi2 = 0.5194

Survival analysis: Crude hazard ratio: Hospitals (Fluticasone, polyp recurrence) (hospital1=GSh, hospital2=Panorama)

```
. xi: stcox i.hospital
i.hospital        _Ihospital_1-2      (_Ihospital_1 for hospital==GSH omitted)

         failure _d:  recur
   analysis time _t:  survivaltime
                 id:  id

Iteration 0:   log likelihood = -23.450105
Iteration 1:   log likelihood = -23.241784
Iteration 2:   log likelihood = -23.241769
Refining estimates:
Iteration 0:   log likelihood = -23.241769

Cox regression -- no ties

No. of subjects =           29                 Number of obs   =        29
No. of failures =           12
Time at risk    =        16815
                                               LR chi2(1)      =      0.42
Log likelihood  =   -23.241769                 Prob > chi2     =    0.5186

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_Ihospital_2 |   1.460527   .8635516     0.64   0.522     .4583823    4.653624
------------------------------------------------------------------------------
```

Log rank test for equality of survivor functions: Smell recovery

spraynew	Events observed	Events expected
Beclomethasone	5	4.13
Fluticasone	15	14.03
Mometasone	6	7.84
Total	26	26.00

chi2(2) = 0.79
Pr>chi2 = 0.6724

Survival analysis: Crude hazard ratio: Smell recovery
(spraycat1=beclomethasone, spraycat2=fluticasone, spraycat3=mometasone)

```
. xi: stcox i.spraynew
i.spraynew        _Ispraynew_1-3      (naturally coded; _Ispraynew_1 omitted)

         failure _d:  smell
   analysis time _t:  survivaltime
                 id:  id

Iteration 0:   log likelihood = -79.721678
Iteration 1:   log likelihood = -79.311946
Iteration 2:   log likelihood =  -79.30966
Iteration 3:   log likelihood =  -79.30966
Refining estimates:
Iteration 0:   log likelihood =  -79.30966

Cox regression -- no ties

No. of subjects =           58                     Number of obs    =        58
No. of failures =           26
Time at risk    =        31688
                                                   LR chi2(2)       =      0.82
Log likelihood  =    -79.30966                     Prob > chi2      =    0.6623
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Ispraynew_2	.8598791	.4589069	-0.28	0.777	.3021075	2.447447
_Ispraynew_3	.5845533	.3811863	-0.82	0.410	.1628384	2.098415