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Table of Contents

Editorial

Natural Orifice Transluminal Endoscopic Surgery

Christian Camenzuli

Surgery underwent a tremendous revolution in the past two centuries. From what was a barbaric death sentence in the 19th century, through the invention of anesthesia, antisepsis and improved surgical technique, it is now a profession that offers the hope of cure to many patients.[1] Today the focus of progress within this field is lead by offering a faster less painful recovery whilst making interventions safer and preferably scarless.[2] These aims are being reached by developments in endoscopic technology and it is within this historic background that the concept of natural orifice transluminal endoscopic surgery (NOTES) has developed.

The original understanding of NOTES dates back to almost two decades ago. It promotes the ability to perform surgical procedures after gaining access from natural cavities. The original operations considered included transgastric cholecystectomy and transgastric appendectomy. These procedures were carried out with flexible instruments and a number of problems were encountered. They included having reliable closure of the opened viscus, prevention of infection, maintaining spatial orientation, having appropriate devices and tools to work with and difficulties with the management of intra-abdominal complications.[3]

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Flexible instruments used in the original concept of NOTES limit the ability of the surgeon to perform efficient dissection of tissues, consequently prolonging the time of surgery to the point that the procedure does not remain minimally invasive. Research has been directed to develop new flexible instruments as part of working platforms so as to facilitate the execution of pure NOTES techniques.[4] These instruments however have not caught up with the rapid progress of surgical techniques. The latter, together with many other difficulties including problems with training surgeons to perform the procedures safely and efficiently, has led the drive to perform NOTES to lose momentum.

Today NOTES techniques are being integrated with established laparoscopic (using rigid instruments) and robotic techniques in what is being called Hybrid NOTES. Some examples of Hybrid NOTES procedures that have reached routine clinical practice in some centers include transvaginal/transanal hybrid NOTES colect omy,[5-6] transanal total mesenteric excision (TaTME),[7] transvaginal hybrid NOTES appendectomy[8] and transvaginal hybrid NOTES cholecystectomy.[9]

Published literature so far shows that using a Hybrid NOTES technique offers patients less post-operative pain with a superior cosmetic result.[10] These techniques are at the forefront of surgical care today and are the most likely direction NOTES will take in the near future.[11]

References

1. Gawande A. 2012. Two Hundred Years of Surgery. NEJM 366, pp1716-23.
2. Mack M. 2001. Minimally invasive and robotic surgery. *JAMA* 285(5), pp568-572. doi:10.1001/jama.285.5.568.
3. Rattner D, Kalloo and ASGE/SAGES Working Group. 2006. ASGE/SAGES Working Group on Natural Orifice Translumenal Endoscopic Surgery. October 2005. Surgical endoscopy 20(2), pp329-33.
4. Lee H., Kim K., Seo J. and Sohn D. 2017. Natural orifice transluminal endoscopic surgery with a snake-mechanism using a movable pulley. *International journal of medical robotics and computer assisted surgery* doi: 10.1002/rcs.1816.
5. Senft J., Warschkow R., Diener M., Tarantino I., Steinemann D., Lamm S., Simon T., Zerz A., Müller-Stich B. and Linke G. 2014. The transvaginal hybrid NOTES versus conventionally assisted laparoscopic sigmoid resection for diverticular disease (TRANSVERSAL) trial: study protocol for a randomized controlled trial. *Trial* 20(15), pp454. doi: 10.1186/1745-6215-15-454.
6. Fuchs K., Breithaupt W., Varga G., Schulz T., Reinisch A. and Josipovic N. 2013. Transanal hybrid colon resection: from laparoscopy to NOTES. *Surgical endoscopy* 27(3), pp746-52. doi: 10.1007/s00464-012-2534-7
7. Xu W., Xu Z., Cheng H., Ying J., Cheng F., Xu W., Cao J. and Luo J. 2016. Comparison of short-term clinical outcomes between transanal and laparoscopic total mesorectal excision for the treatment of mid and low rectal cancer: A meta-analysis. *European journal of surgical oncology* 42(12), pp1841-1850. doi: 10.1016/j.ejso.2016.09.002.
8. Bernhardt J., Steffen H., Schneider-Koriath S. And Ludwig K. 2015. Clinical NOTES appendectomy study: comparison of transvaginal NOTES appendectomy in hybrid technique with laparoscopic appendectomy. *International journal of colorectal disease* 30(2), pp259-67. doi: 10.1007/s00384-014-2081-x.
9. Dhillon K., Awasthi D. And Dhillon A. 2017. Natural orifice transluminal endoscopic surgery (hybrid) cholecystectomy: The Dhillon technique. *Journal of minimal access surgery* 13(3), pp176-181. doi: 10.4103/0972-9941.207838.
10. Steinemann D., Müller P., Probst P., Schwarz A., Büchler M., Müller-Stich B. and Linke G. 2017. Meta-analysis of hybrid natural-orifice transluminal endoscopic surgery versus laparoscopic surgery. *British Journal of Surgery* 104(8), pp977-989. doi: 10.1002/bjs.10564.
11. Bernhardt J., Sasse S., Ludwig K. and Meier P. 2017. Update in Natural Orifice Translumenal Endoscopic Surgery (NOTES). *Current opinion in gastroenterology* 33(5), pp346-351. doi: 10.1097/MOG.0000000000000385.

Cover Picture:
'Rough seas'
Oil on canvas with palette knife
By Victor Grech

Victor Grech is a consultant paediatrician with a special interest in paediatric cardiology. He has a PhD in this field and another in science fiction. He is the editor of the journals Images in Paediatric Cardiology and the Malta Medical Journals and co-chairs HUMS, the Humanities, Medicine and Sciences Programme at the University of Malta.

Original Article

Can pterygium excision with mitomycin C leaving bare sclera be salvaged?

James Vassallo, Suzanne T Pirotta, Gabriella M Sciriha, Maria De Bono Agius, Mario Vella

Abstract

Purpose: The aim of this study was to analyze the recurrence rate of pterygium following excision with intra-operative mitomycin C (MMC) and post-operative scraping of the perilimbal conjunctival defect, and the patients' satisfaction with this technique.

Methods: This is a retrospective analysis of a cohort of 33 eyes of 28 patients with primary or recurrent pterygium who underwent simple excision with MMC. They were followed up after a mean of 27.8 months. The main outcomes considered were the recurrence rate and patient satisfaction. A recurrence was defined as any regrowth of conjunctiva over the limbus and any complications were considered significant. The patients were interviewed with a standard questionnaire and examined.

Results: An objective recurrence was noted in 55% (18 out of 33 eyes). The recurrence rate after excision of primary pterygia was 46% (13 out of 28 eyes), and for recurrent pterygia it was 80% (four out of five eyes). In this study the complications included: six eyes that developed a granuloma, one case of bleeding which persisted for three days post-op, and one eye in which there was a suspected scleral melt at five weeks. 79% of the procedures resulted in a good patient satisfaction (26 out of 33 eyes), and only in 15% (five eyes) was there a subjective recurrence.

Conclusions: This technique in our study resulted in an unacceptably high recurrence rate, especially in the case of recurrent pterygia. However, patients still tended to be satisfied with the outcome.

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Keywords

mitomycin C; MMC; pterygium; recurrence.

Introduction

A pterygium is a superficial, usually elevated, wing-shaped fold of conjunctiva that grows over the limbus and extends onto the corneal surface. Pterygia can vary from small, atrophic, quiescent lesions to large, aggressive, rapidly-growing fibrovascular lesions that can distort the corneal topography, and in advanced cases, obscure the optical centre of the cornea.

Pterygia are described as a proliferative disorder resembling an aberrant wound healing response.[1] It is a disease of limbal stem cells which are damaged primarily by chronic UV light exposure causing up-regulation of the p53 tumour suppressor gene. This leads to decreased apoptosis, increased activity of matrix metalloproteinases resulting in Bowman's layer dissolution, activation of cytokines and growth factors resulting in leukocytic infiltration, and activation of fibroblasts causing increased elastin deposition. The limbal predilection may be explained by the phenomenon

of peripheral light focusing, in which incident light passes through the anterior chamber and is focused at the distal (nasal) limbus where limbal stem cells reside.

Typically, a pterygium consists of three distinct parts: cap, head, and body/tail. The cap or leading edge is a flat zone on the cornea that consists mainly of fibroblasts that invade and destroy Bowman's layer. The head is a vascular area that lies behind the cap and is firmly attached to the cornea. The body/tail is the mobile area of the bulbar conjunctiva, which can be easily dissected from the underlying tissue. Lesions larger than 3.5mm on the cornea are likely to be associated with more than one dioptre of astigmatism.

The main indications for surgical removal are: discomfort despite lubricants, decreased vision, diplopia, and cosmetic intolerance. Several surgical techniques exist and the best method would ideally have the least rate of recurrence and a short operating time. Techniques used are:

- Bare sclera technique – this has the highest rate of recurrence but relatively short operating time.[2]
- Conjunctival autograft technique – using sutures, fibrin glue, or autologous blood to fix the graft onto the scleral bed[3]; associated with less recurrence rate but longer operating time.
- Amniotic membrane graft (AMG) – fixed using sutures or fibrin glue; it is a useful alternative to conjunctival autografting especially in patients who have limited amount of conjunctiva. However, there is the issue of availability of such materials and most studies report a significantly higher rate of recurrence with AMG.[4]

Adjunctive therapies include the use of intraoperative mitomycin C (MMC) due to its anti-fibrotic and anti-angiogenic properties, or β-radiation; the latter is no longer in use due to its adverse effects on the eye.

MMC alkylates and cross-links DNA, and inhibits DNA, RNA, and protein synthesis. It probably has a long-term influence on cellular proliferation.[5] It is thus used as a fibroblast inhibitor. The use of topical MMC as an adjunct to pterygium surgery was first introduced by Kunitomo and Mori in Japan and subsequently by Singh *et al*.[6] Recurrence rates are reported to be 5.4–21% when MMC is used alone in treating primary pterygium and 12.5–19.2% when treating recurrent pterygium.[7] Various studies have shown that using MMC in patients with more severe pterygia as an adjunct to conjunctival autografting, lowers the recurrence rate.

In this study we are investigating the outcome with the bare sclera technique augmented with intra-operative MMC, followed by post-operative scraping of the scleral bed until corneal re-epithelialization.

Methods

This is a retrospective analysis of a cohort of 33 eyes of 28 patients who underwent primary or recurrent pterygium excision with intra-operative MMC in the same institution between November 2011 and December 2013. The procedures were carried out by six different surgeons – one consultant and five different trainees of varying experience (Table 1).

***Table 1**: Breakdown of the surgeons involved according to surgical experience*

Level of experience	Number of procedures
Consultant	4
Young trainee 1	1
Young trainee 2	1
Senior trainee 1	9
Senior trainee 2	9
Senior trainee 3	9

The patient list was obtained from the database supplied by the surgical performance unit of the hospital. Formal ethics and data access approvals were granted. The patients were selected sequentially from the list in chronological order. The inclusion criterion was pterygium excision with intra-operative MMC and post-operative scraping as explained in this section. Exclusion criteria were: incomplete information including poor documentation, patients lost to follow-up and those who could not be contacted or come for the examination, and patients in whom the method of excision was different from the one described below.

***Table 2**: Data entry form devised for this study*

ID
Name & Surname
Age now
Procedure details
Side
Date of procedure
Surgeon performing procedure
Months since procedure
Duration of pterygium prior to excision
Is indication for surgery clearly documented?
Pre-op VA
Pre-op size documented
Pre-op size /mm
Primary / recurrent pterygium
Biopsy submitted Y/N
Indication for surgery: Objective Subjective
Pain / foreign body sensation during surgery 0-10
Pain / discomfort post-op (during recovery) 0-10
Pain / foreign body sensation during post-op scrapings 0 - 10
No. of scrapings
Timing of scraping (days post-op)
Duration of post-op antibiotic & steriod regimen
Antibiotic & steriod regimen
Post-op lubricants Y/N
Peri-op complications
Post-op complications
Is the patient happy with the result?
Would the patient do this procedure again for a pterygium in the other eye?
Would the patient do this procedure again for a pterygium in the same eye?
Sunglasses being used regularly in the sun Y/N
Lubricants being used Y/N
Subjective recurrence Y/N
VA post-op (from file) and/or today
Objective recurrence Y/N
Size of recurrent pterygium, if present
Examination findings
Other remarks

The notes of the patients included in the study were reviewed, and the patients were called for questioning throughout the year 2015. A questionnaire devised by the study group was used (Table 2), and the patients were examined to assess for recurrent growth. As shown in Table 2, patients were also asked about use of lubricating drops and UV protection with sunglasses. A recurrence was defined as any growth of conjunctiva beyond the limbus. Patients were asked to recall the discomfort felt on scraping of the scleral bed carried out during the early post-operative reviews under topical anaesthesia with 0.4% oxybuprocaine.

The procedures were all done under local anaesthesia using topical 0.4% oxybuprocaine and subconjunctival 2% lignocaine with 1:200,000 adrenaline. The pterygium was excised from the cornea under an operating microscope, with attention to remove as much fibrovascular tags as possible. The excision included the adjacent thickened bulbar conjunctiva and underlying Tenon's capsule. This was followed by the application of 0.04% mitomycin C for two minutes on the scleral bed using soaked spear swabs avoiding contact with the limbus and cornea, followed by immediate copious irrigation of the conjunctival sac.

The typical post-operative regimen was a 1% chloramphenicol ointment patch till the following day. The patients were closely monitored early on and scraped as needed in an attempt to achieve healing of the cornea before the perilimbal conjunctival defect. The patients were mostly reviewed the first time on day 1-2 and the slough developing on the scleral bed was scraped away from the limbus with a cotton tip or the side of a wide-bore needle/blade. Further scraping was repeated until the corneal epithelium healed completely. The typical treatment prescribed was a combination of 0.3% tobramycin and 0.1% dexamethasone as ointment bd and as drops qds for 3-4 weeks.

Results

The male-to-female ratio was 3:1 and the mean age was 59.4 years (range: 31-86 years). There were four temporal pterygia, and five recurrent nasal pterygia. The patients were followed up after a mean of 27.8 months (SD: 8.9 months; maximum follow-up: 44 months).

The mean time that the patient spent in theatre

was 25 minutes (SD: 8.6 minutes; range: 15-45 minutes).

In this study the complications included: six eyes that developed a granuloma, one case of bleeding which persisted for three days post-op, and one eye in which there was a suspected scleral melt at five weeks. The granulomas were treated first-line with intensive application of topical steroids, and the case of possible melting was managed with a conjunctival advancement.

An objective recurrence was noted in 55% (18 out of 33 eyes). This included minimal overgrowth on the cornea. The recurrence rate after excision of primary pterygia was 46% (13 out of 28 eyes) and for recurrent pterygia it was 80% (four out of five eyes). The earliest recurrence was documented at four months.

Data on patient satisfaction showed that 79% were happy with the result (26 out of 33 eyes), and only 15% had noted a recurrence (five eyes). 88% said that they would be happy to do same procedure again on the same eye if a recurrent pterygium were to be removed. During the post-operative scrapings the mode pain score was 0/10, with a mean of 1/10.

Figure 1 shows the breakdown of subjective and objective indications for excision in our group of patients.

In the group of patients studied, only one excision specimen was submitted for histology. This was a case of a bilobed pterygium and it was submitted to exclude possible carcinoma due to the temporal component. Features characteristic of a pterygium were confirmed by the pathologist.

Only 24% said that they used lubricating drops post-op (eight out of 33 eyes).

Discussion

Over the past couple of decades, there has been a significant advancement in pterygium surgery techniques that has led to an increased variety of options available for the ophthalmic surgeon. In this study, MMC was used intra-operatively and patients were monitored closely post-operatively with conjunctival scraping if needed, in an attempt to achieve healing of the corneal epithelium before that of the perilimbal conjunctiva.

Data collected in this study reports an objective recurrence in 55% (18 out of 33 eyes). While the recurrence rate after excision of primary pterygia was 46% (13 out of 28 eyes), that for recurrent pterygia was reported to be 80%. The fact that 79% of patients were satisfied with the result indicates that the patients were asymptomatic.

The use of high cumulative doses of MMC post-operatively, as well as poor selection of patients, can lead to the development of severe complications. To limit these complications, it is of utmost importance to set strict exclusion criteria, to use MMC only intra-operatively under controlled conditions, and to follow the patients closely until ocular surface re-epithelialization is complete.[8]

Patients suffering from conditions that predispose to poor wound healing should not be treated with MMC. These include patients with atopic keratoconjunctivitis, severe dry eye, acne rosacea, and herpes keratitis. Possible complications that can arise from the uncontrolled use of MMC or its use in high-risk patients include: corneal oedema or perforation, corectopia, iritis, scleral calcification, pain, secondary glaucoma, and cataract.[9]

Varying concentrations of MMC have been used intra-operatively, usually in the range of 0.02-0.04%. Also, the time of exposure of MMC to the subconjunctival space varies in different studies, usually from one to five minutes. In this study, the concentration of MMC used was 0.04% and the intra-operative exposure time was two minutes. This large variation makes it difficult to compare the results. The safest concentration and exposure time of intra-operative MMC that are effective in preventing pterygium recurrence without causing complications have still not been established. More large-scale prospective studies will need to be carried out to reach a conclusion.

Table 3 summarizes the findings of a meta-analysis carried out by Sanchez-Thorin *et al*,[10] and studies by Manning and Young.[11-12] In the latter two studies, the sclera was covered by conjunctiva at the end of the procedure.

Pterygium excision with conjunctival autograft is time-consuming and has a significant learning curve. Surgeons may also be reluctant to use a conjunctival autograft in patients who may need the conjunctiva for future surgical procedures. On the other hand, avoiding the use of MMC will not expose the patients to its possible side-effects, even though these are uncommon when MMC is used appropriately.

***Figure 1**: Indications for pterygium excision: Chart 1a - Subjective; Chart 1b – Objective*

Chart 1 a – Subjective

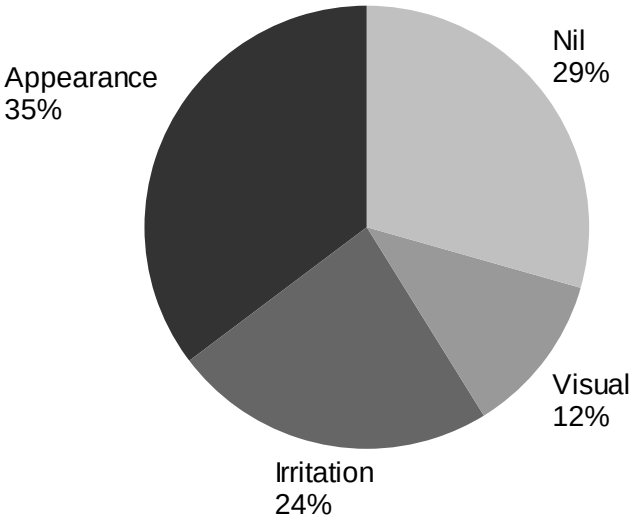
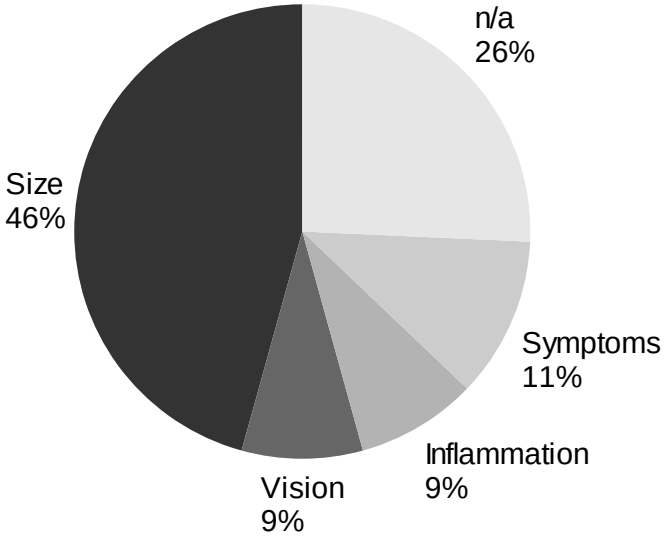


Chart 1 b – Objective



In our study, the rate of recurrence in primary pterygia was 46%. However, this percentage also included minimal overgrowth on the cornea (<1mm), therefore comparison to these studies is difficult since the definition of recurrence varied. For example, some defined recurrence as a regrowth of >1.5mm.[11] However, a recurrence actually starts when there is a reactivation of the inflammatory process (vascular congestion and thickening) in the treated area.[13] It should be noted that our first recurrence was documented at four months, even though usually recurrences occur in the first three months after excision.[14] Our method could thus have retarded the recurrence. Further studies would be needed to establish whether this effect is statistically significant.

Also, one has to take into consideration the high UV index the Maltese population is exposed to throughout the year (Mediterranean climate), the ever-increasing environmental pollutants, and possible genetic factors that may influence recurrence rates.

As mentioned previously, pterygium excision with conjunctival autograft is time-consuming and has a steep learning curve. Variations to this procedure include the use of intra-operative MMC combined with closure of the conjunctiva to the limbus, thus avoiding bare sclera. This was reported to give good results and at the same time decrease the possible complications caused by MMC.[15] In addition, this approach does not increase the procedure time significantly, therefore providing a good compromise.

***Table 3**: Summary of findings of a meta-analysis by Sanchez-Thorin et al 1998 (12)*

Author	Year of publication	Technique	Number of Eyes	MMC concentration (%)	MMC contact time (minutes)	Recurrence rate (%)
Lewallen	1989	Bare sclera	16	n/a	n/a	40.0
Chen *et al*	1995	Bare sclera	17	n/a	n/a	88.2
Singh *et al*	1988	Bare sclera	18	n/a	n/a	88.9
Mahar, Nwokora	1993	Bare sclera	15	n/a	n/a	60.0
Manning *et al*	1997	Intra-operative MMC	19	0.04	3	10.5
Young *et al*	2004	Intra-operative MMC	53	0.02	5	15.9
Chen *et al*	1995	Conjunctival autograft	23	n/a	n/a	39.1
Lewallen	1989	Conjunctival autograft	17	n/a	n/a	17.6
Manning *et al*	1997	Conjunctival autograft	18	n/a	n/a	22.2
Young *et al*	2004	Conjunctival autograft	52	n/a	n/a	1.9
Manning *et al*	1997	Post-operative MMC	19	0.02	qds x1 wk	21.1
Chen *et al*	1995	Post-operative MMC	24	0.02	bd x5 days	37.5
Mahar, Nwokora	1993	Post-operative MMC	17	0.04	qds x2 wks	0

The main strength of this study is the long follow-up period. However, there were several limitations in this study. The sample size was small, and having different surgeons produces operator bias. With multiple surgeons there is variation in technique, and procedures carried out by trainee surgeons at different stages in their training were included. It is difficult to standardize quality of excision, even by the same surgeon. In addition, since this was a retrospective study, there is a likelihood of recall bias by the patients when they were questioned regarding their experience; a prospective approach would have been better to decrease recall and selection bias, and improve the quality of the data. A visual analogue pain scale could have been better suited for patients to grade pain. Also, it is difficult to ensure patient compliance with the post-operative treatment and precautions. This is important since limited use of post-operative topical steroid is associated with a higher risk of recurrence.[16] There are other confounding factors which influence the risk of recurrence, such as sun exposure and dry eye disease, but these are very difficult to control.

In our study the recurrence rate after recurrent pterygium excision was very high and this indicates that MMC alone is not sufficient for recurrent pterygia; even the overall recurrence rate was

unacceptably high. However, for patients who are unlikely to tolerate a long operation time for various reasons, this method remains an option, provided that the patient is aware of the higher recurrence rate.

Possible improvements on the intra-operative MMC method may be: increasing the MMC exposure time, and meticulous clearance of the limbus to remove all the vascular bridges.

The use of lubricants and sunglasses should be encouraged, especially in early pterygia and following excision, as this can decrease symptoms and possibly slow progression or recurrence.

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References

1. Chui J, Coroneo MT, Tat LT, Crouch R, Wakefield D, Di Girolamo N (2011) Ophthalmic Pterygium: A Stem Cell Disorder with Premalignant Features. American Journal of Pathology 178(2):817–27.
2. D'Ombrain A (1948) The Surgical Treatment of Pterygium. Br J Ophthalmol 32(2):65–71.
3. Sirisha G, Jyothi S, Chowdary NL (2016) Autologous Blood For Conjunctival Autograft Fixation in Pterygium Surgery. Indian Journal of Applied Research 6(4):328-30.
4. Prabhasawat P, Barton K, Burkett G, Tseng SC (1997) Comparison of conjunctival autografts, amniotic membrane grafts, and primary closure for pterygium excision. Ophthalmology 104(6):974-85.
5. Verweij J, Pinedo H (1990) Mitomycin C: mechanism of action, usefulness and limitations. Ant-Cancer Drugs 1(1):5-13.
6. Singh G, Wilson M, Foster C (1998) Mitomycin eye drops as treatment for pterygium. Ophthalmology 95:813-20.
7. M R Fallah, M R Golabdar, J Amozadeh, M A Zare, S Moghimi and G Fakhraee (2008) Transplantation of conjunctival limbal autograft and amniotic membrane vs mitomycin and amniotic membrane in treatment of recurrent pterygium. Eye 22:420–4.
8. Frucht-Pery J, Ilsar M (1994) The use of low-dose mitomycin C for prevention of recurrent pterygium. Ophthalmology 101:7597-662.
9. Singh G, Wilson M, Foster C (1990) Long term follow up study of mitomycin eye drops as adjunctive treatment of pterygia and its comparison with conjunctival autograft transplantation. Cornea 9:331-4.
10. Sánchez-Thorin JC, Rocha G, Yelin JB (1998) Meta-analysis on the recurrence rates after bare sclera resection with and without mitomycin C use and conjunctival autograft placement in surgery for primary pterygium. Br J Ophthalmol 82:661–5.
11. Manning C, Kloess P, Diaz M (1997) Intraoperative mitomycin in primary pterygium excision. A prospective randomised trial. Ophthalmology 104:844-8.
12. Young A, Leung GY, Wong AK, Cheng LL, Lam DS (2004) A randomised trial comparing 0.02% mitomycin C and limbal conjunctival autograft after excision of primary pterygium. Br J Ophthalmol 88:995-7.
13. Vergés C (2012) Recurrent pterygium, how to diagnose and how to treat. Available at https://pterigion.net/2012/11/29/recurrent-pterygium-how-to-diagnose-and-how-to-treat/. Accessed 06 June 2016.
14. Lewallen S (1989) A randomized trial of conjunctival autografting for pterygium in the tropics. Ophthalmology 96(11):1612-4
15. Raiskup F, Solomon A, Landau D, Ilsar M, Frucht-Pery J (2004) Mitomycin C for pterygium: long term evaluation. Br J Ophthalmol 88(11):1425-8.
16. Yaisawand S, Piyapattanakorn P (2003) Role of post-operative topical corticosteroids in recurrence rate after pterygium excision with conjunctival autograft. J Med Assoc Thai. 86 Suppl 2:S215-23.

Original Article

Assessing the analgesic benefit of phacoemulsification under topical anesthesia using pre-operative nepafenac 0.1%

Matthew Fenech, Thomas Fenech

Abstract

Background: To compare the intra-operative analgesic benefit of cataract surgery under topical anesthesia with and without pre-operative NSAIDs, namely nepafenac 0.1% (Alcon Laboratories Inc, Nevanec®, Fort Worth, TX, USA)

Method: In a study carried out at Mater Dei Hospital, Ophthalmic department, Malta, 199 patients with a cataract were divided into two groups. 100 eyes received nepafenac 0.1% pre-operatively while 99 eyes did not. Intra-operative discomfort was judged by assessing facial grimacing, restlessness, irritability and distress and the results were noted. Patients were divided into refractive error groups, namely myopic, hypermetropic and emmetropic.

Results: Pre-operative nepafenac 0.1% produced significantly more pain free cataract surgeries, resulting in a discomfort rate of 9% vs 28% in the group where pre-operative nepafenac 0.1% was not used. Pain was also most evidently observed on insertion of the phaco handpiece. This may be said for patients in all refractive errors groups.

Conclusions: The analgesic efficacy of nepafenac 0.1% pre-operatively is significant in reduced intra-operative discomfort during cataract surgery repair under topical analgesia.

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Keywords

NSAIDs, Nevanac®, nepafenac 0.1%, topical anesthesia, myopia, phacoemulsification

Introduction

Nepafenac 0.1% (Alcon Laboratories Inc, Nevanac®, Fort Worth, TX, USA) is an ophthalmic NSAID. It has a prodrug structure, making it a neutral molecule. This property allows it to penetrate the cornea, after which it is converted by intraocular hydrolases to its more active moiety amfenac.[1] Nepafenac is unique, in that its bioconversion to amfenac is targeted to the iris and ciliary body and, to an even greater extent, the retina and choroid.

Like other NSAIDs, nepafenac works by inhibiting the synthesis of prostaglandins. While we are aware of the beneficial implications of NSAIDs in reducing post-operative inflammation and its sequelae such as cystoid macular oedema, not much is yet known about how pre-operative NSAIDs possibly have an effect in reducing intra-operative discomfort.

The primary objective of this study was to assess the effect of pre-operative nepafenac 0.1% on the effects of intra-operative discomfort in cataract surgery performed under local anaesthetic. Secondary outcomes included defining the stage at which discomfort was most likely to be experienced and the impact of refractive error on the degree of discomfort experienced.

Materials and Methods

This observational study was performed at Mater Dei Hospital Malta between January 2014 and January 2016. The study included 196 patients (199 eyes) who underwent phacoemulsification surgery by the same consultant surgeon. 100 eyes were operated on after application of pre-operative topical anesthesia using oxybuprocaine 0.4% while 99 eyes were operated on after application of pre-

operative oxybuprocaine 0.4% and nepafenac 0.1%. All procedures were performed by the same consultant surgeon.

The study was approved by the appropriate patient safety and ethics approval boards. All patients underwent an extensive pre-operative assessment.

Strict inclusion and exclusion criteria were established. Patients being unfit for surgery were excluded from the study cohort. Patients with contra-indications to non-steroidal anti-inflammatory medication or who were already on regular pain relief were not considered for the purpose of the study. Patients, who had communication problems, were unable to co-operate during pre-operative assessment or who were deemed excessively photophobic or expected to endure excessive discomfort due to prolonged surgery or pupils which were difficult to dilate were excluded from the study, necessitating surgery under general anesthesia.

All patients were advised on the steps of the procedure, the expected duration and the importance of relaxing throughout the procedure. Patients were advised to keep their eyes open throughout the procedure, avoiding excessive eye movement at all times. Patients were consented before the procedure and all patients who failed to provide their consent were excluded from the study.

All patients were brought in the morning of the procedure. 100 eyes were instilled with 2 drops of oxybuprocaine 0.4% 5 minutes before the procedure. 99 eyes were also given 2 drops of nepafenac 0.1% 1 hour before the procedure. Patients who were excessively anxious or suffered severe pain during the procedure were given retrobulbar blocks. Top-up topical anaesthetic was also used. Such patients were considered as clear failures to the success of both pre-operative nepafenac 0.1% and oxybuprocaine0.4%. No effort was made to randomize the pre-operative nepafenac 0.1% group from the group that did not receive such NSAIDs.

All procedures were performed by the same consultant ophthalmic surgeon. The Infinity Phacoemulsification Machine by Alcon was used throughout the study. Patients underwent the same three stage approach; capsulorrhexis, hydrodissection and phacoemulsification, followed by IOL insertion. An effort was made to maintain the same size of main incision whilst also making use of the same phaco pressures as these may influence the discomfort experienced. Foldable posterior chamber intra-ocular lenses by Alcon were used.

Intra-operative and post-operative discomfort was assessed by the same consultant surgeon. Verbal response, restlessness and facial grimacing observed were used to identify any discomfort. An official pain score scale by patients was not utilized in order to avoid patient variability and bias.

Results

A total of 199 eyes were used for this study. Only patients who completed the surgery without intra-operative complications were deemed fit to be included in the study.

The mean age of patients used in the study was 76 years, with ages ranging from 32 years to 90 years of age. Over 95% of patients were Caucasian. 108 of the eyes belonged to female patients and 91 belonged to male patients. There was no significant difference in the degree of discomfort witnessed between male and female patients.

Discomfort was witnessed in 28% of patients who were not provided with pre-operative nepafenac 0.1% but in only 9% of patients to whom nepafenac 0.1% was given pre-operatively *(Figures 1-3)*. By using Fisher's exact test, the results prove to be statistically significant, with a P value of 0.0009.

In both groups, discomfort was most evident in the myopic sub-group, with 22.2% of myopic patients in the pre-operative nepafenac 0.1% group experiencing some form of discomfort as opposed to 37.5% of myopes who were not given nepafenac 0.1% pre-operatively. Furthermore, the greater the degree of myopia observed, the greater the degree of perceived discomfort. Least discomfort was evident in the hypermetropes, with discomfort evident in 2.6% of patients in the pre-operative NSAID subgroup and 4.3% of patients who were not given pre-operative nepafenac 0.1% *(Figure 4)*.

Irrespective of one's refractive error, discomfort was most evident on insertion of the phaco-handpiece, amounting to 72.7% of all the discomfort felt throughout the cohort. Such a pattern was evident in all refractive error groups in both those patients treated with or without pre-operative nepafenac 0.1%. Least discomfort was noted on insertion of the intra-ocular lens (IOL) *(Figure 5)*.

Figure 1: *Graph showing the percentage of discomfort witnessed in each refractive error group in patients who were not given pre-operative topical NSAIDs. Discomfort being most evident in the myopic sub-group.*

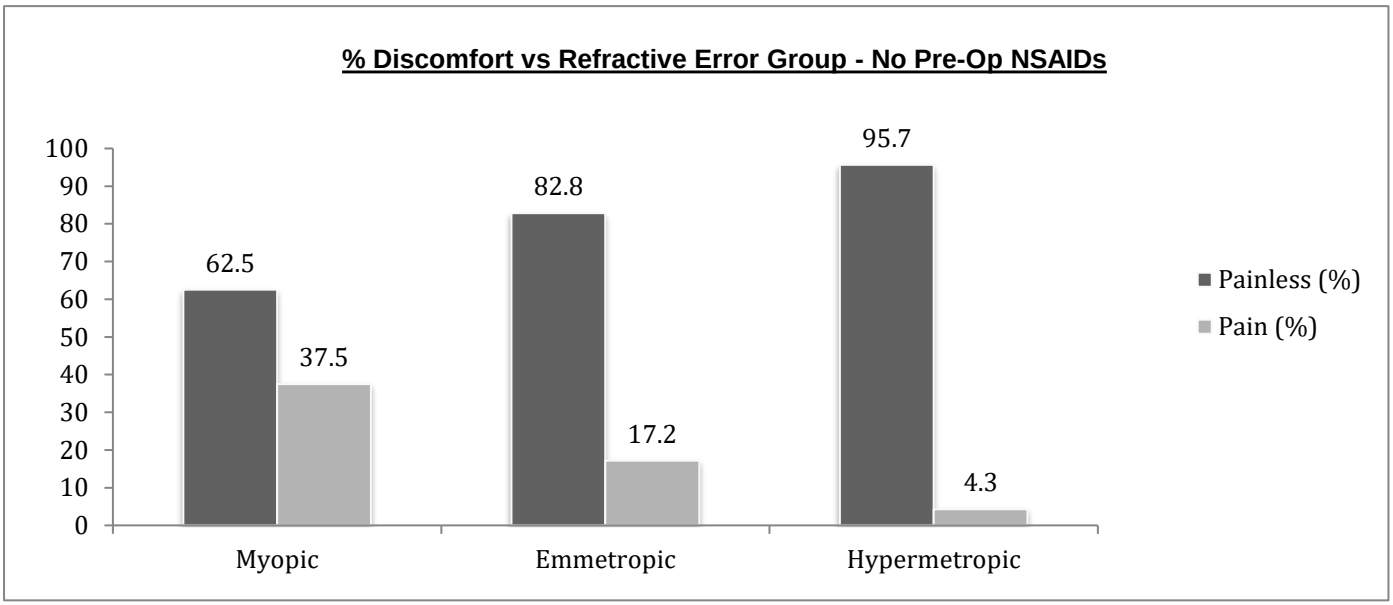


Figure 2: *Graph showing the percentage of discomfort witnessed in each refractive error group in patients who were given pre-operative topical NSAIDs. Discomfort being most evident in the myopic sub-group*

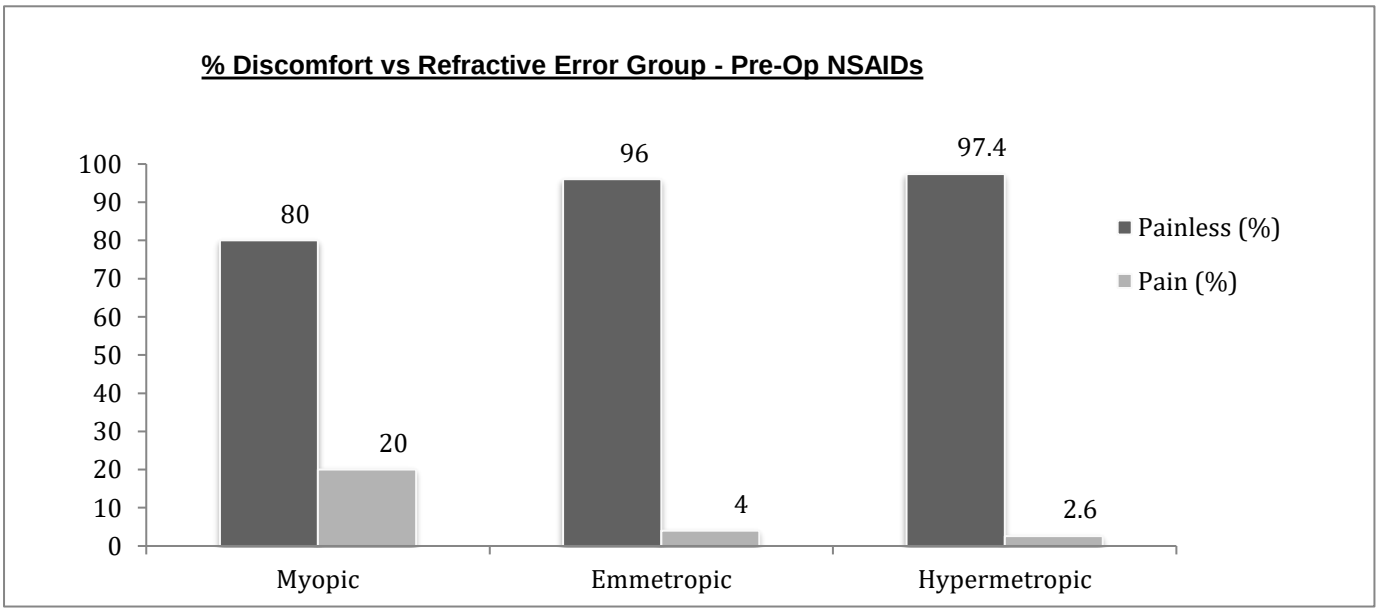


***Figure 3**: Graph showing the percentage of discomfort witnessed in each refractive error group in patients who were given pre-operative topical NSAIDs vs those who were not given pre-operative NSAIDs.*

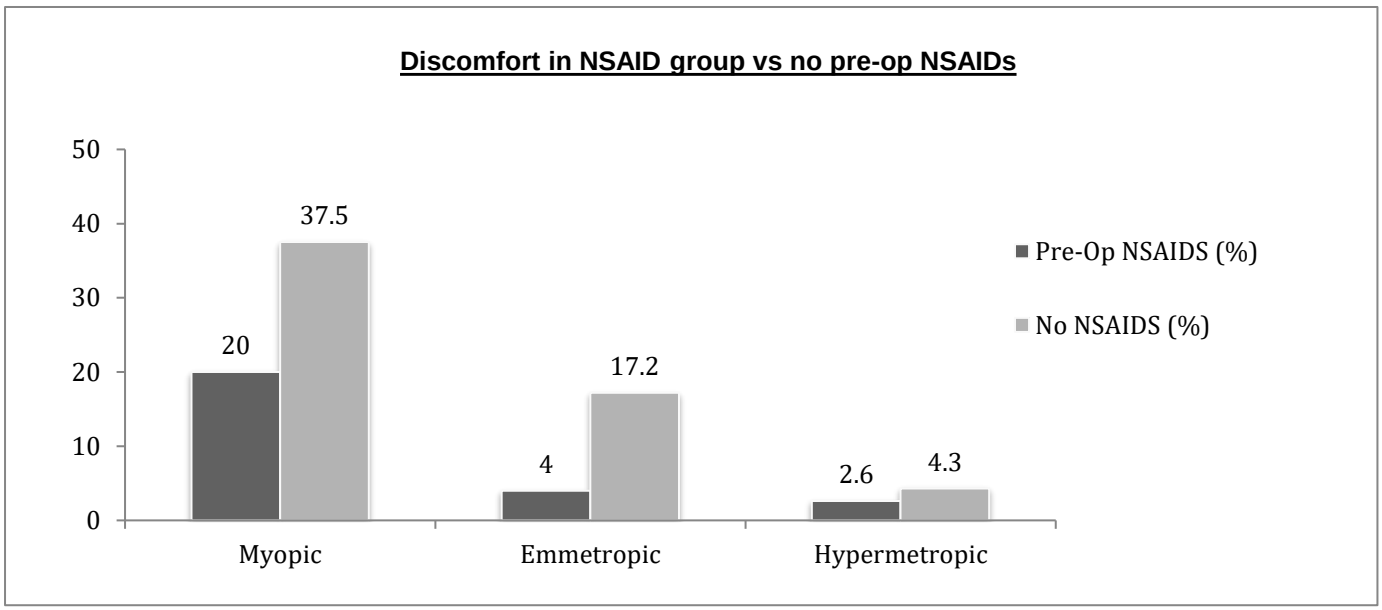


***Figure 4:** Graph showing the increase in discomfort witnessed with increasing myopic severity.*

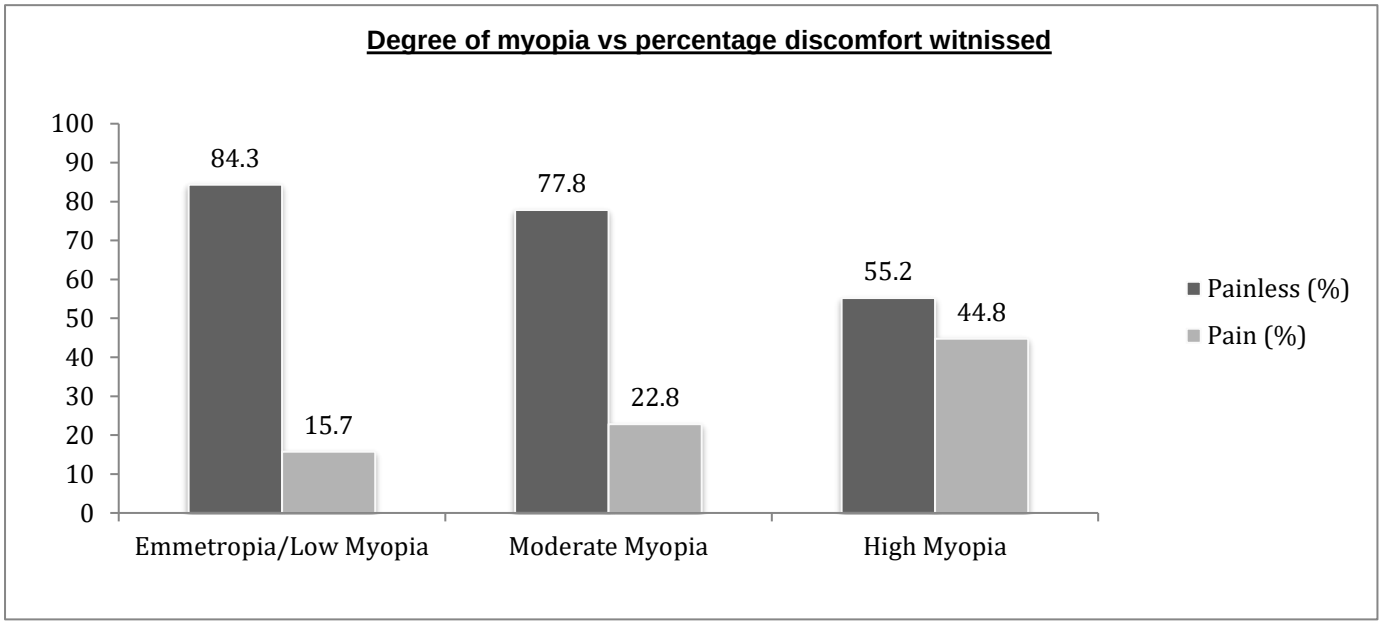
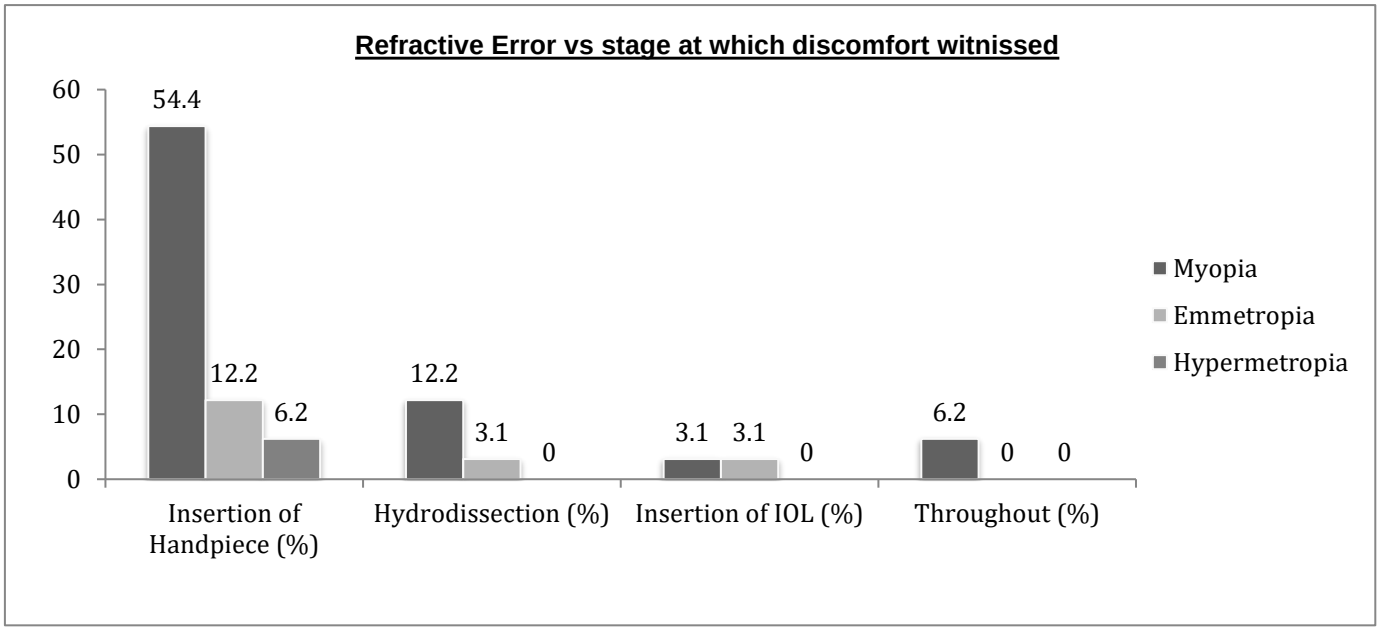


***Figure 5**: Graph showing the stage at which discomfort was witnessed within each refractive error group*



There was no statistical correlation between patient age and perceived intra-operative discomfort. The same may be said for patient sex.

Discussion

Modern day cataract surgery is a quick, relatively painless and routine procedure, performed primarily under local anaesthetic.[2] It involves extraction of the natural lens and replacing it with an artificial intra-ocular lens. The power of the artificial lens is calculated and adjusted pre-operatively.[3] Advances in cataract surgery have meant that this relatively routine procedure has come a very long way since the first recorded procedures in India in the 5th century BC.[4]

Cataract surgery is today performed with the aid of phacoemulsification and is routinely performed under topical anaesthesia. Regional or local anaesthesia is also commonly employed, but recently comparative studies have shown equivalent results in intra-operative and post-operative pain relief.[5]

Topical anaesthesia is commonly performed using ocular anaesthetics, Benoxinate (oxybuprocaine 0.4%) being the most commonly used due to its favorable side effect profile, being less toxic to the corneal epithelium when compared to amide anaesthetics such as lidocaine and bupivacaine. A study by S. Waheeb et.al showed that topical anesthesia solely using topical oxybuprocaine proved to be a safe alternative to retro- or peribulbar injections, being less time consuming and less risky.[6]

Ocular inflammation is a common phenomenon during and after cataract surgery, resulting in intra-operative and postoperative pain. Topical NSAIDs reduce inflammation by reducing prostaglandin synthesis and have been shown to control and reduce inflammation after surgery.[7]

Nepafenac 0.1% was used for the purpose of this study. Unlike other NSAIDs, nepafenac is unique in that it has a prodrug structure, making it a neutral molecule with rapid corneal permeability. The drug is rapidly hydrolyzed to amfenac, the active moiety of the drug. [7] It is understood that such conversion is targeted to the iris and ciliary body. Results from our study reveal that most discomfort is experienced on insertion of the phaco handpiece, the point at which there is a sudden surge in intra-ocular pressure and deepening of the anterior chamber, accompanied by stretching of the zonular fibers. We postulate that the targeted nature of nepafenac 0.1% helps in inhibiting or dampening the pain response felt when such events are set in motion.

Our experience with pre-operative topical NSAIDs has been very encouraging, proving to be extremely beneficial in reducing intra-operative discomfort when compared to using topical oxybuprocaine alone. We postulate that such results are due inhibition of prostaglandin pathways that are immediately activated on manipulation of the

anterior chamber.

It is interesting to note that most discomfort is witnessed in the myopic subgroup at all stages of the procedure. It is unclear as to why such a discrepancy is so evident, especially when one considers the larger nature of the anterior chamber in a myopic eye as opposed to a hypermetropic eye. We postulate that with advanced control of intra-ocular pressure through active fluidics and an IOP ramp, one is able to reduce the overall discomfort observed during cataract surgery, especially when considering that over 70% of discomfort witnessed is on insertion of the phaco handpiece. The IOP ramp will allow a gradual and progressive increase in the IOP as opposed to a sudden surge in IOP during insertion of the phaco handpiece, resulting in a less sudden stretch of the anterior chamber.

Our study is limited in that although strict exclusion and inclusion criteria were implemented, no efforts were made to introduce a control group or a means of blinding. A placebo would have proven beneficial, reducing both performance bias as well as observer bias from the surgeon involved. Whilst this ensures an adequate sample size for both groups of patients by being able to cater for drop outs, it does leave the door open to operator bias. That being said, data was collected over a relatively short period of time, not allowing for changes in operator technique over time, serving to counteract the Hawthorn effect. It is important to note that patients on any source of conflicting extraneous treatment such as any other pain relief medication were excluded for the purpose of this study. Furthermore, although the sample size used was substantial, it must be pointed out that no power calculation was performed in order to assess the true size of the sample needed.

Conclusion

Topical anesthesia is a satisfactory means of pain relief when undertaking phacoemulsification and IOL insertion. Furthermore, pre-operative topical NSAID application reduces discomfort rates in all refractive error subgroups.

There is no association between patient age or sex and discomfort witnessed.

It is evident that the greater the degree of myopia, the greater the rate of discomfort witnessed. Discomfort is also mostly witnessed on insertion of the phaco-handpiece, most prevalent in the myopic sub-group.

References

1. Ke TL, Graff G, Spellman JM, et al. Nepafenac, a unique non-steroidal pro-drug with potential utility in the treatment of trauma-induced ocular inflammation: II. In vitro bioactivation and permeation of external ocular barriers. Inflammation. 2000; 24:371–84.
2. Ashwin PT, Shah S, Wolffsohn JS. Advances in cataract surgery. Clinical and Experimental Optometry 2009; 92(4):333-342
3. Wadbro E, Hellberg P, Schedin S. Optimization of intraocular lens for correction of advanced corneal refractive errors. Applied Optics 2016; 55(16):4378-4382
4. Grzybowski A, Ascaso FJ. Sushruta 600 B.C. introduced extraocular expulsion of lens material. Acta ophthalmologica 2014; 92(2): 194-197
5. Hosoda Y, Kuriyama S, Jingami Y, Hattori H, Hayashi H, Matsumoto M. A comparison of patient pain and visual outcome using topical anesthesia versus regional anesthesia during cataract surgery. Clinical Ophthalmology 2016; 10: 1139-1140.
6. Waheeb S. Topical anesthesia in phacoemulsification. Oman Journal of Ophthalmology 2010; 3(3): 136-139
7. Nardi M, Lobo C, Berecski A, Cano J, Zagato E, Potts S et al. Analgesic and anti-inflammatory effectiveness of nepafenac 0.1% for cataract surgery. Clinical Ophthalmology 2007; 1(4): 27-533
8. de Beketch C, Boissonnot M, Bernit AF, Debaene B, Djabarouti M, Bouamama N, Dighiero P et al. [Simplified anesthesia protocol for cataract surgery under topical anesthesia: one year retrospective study]. Journal francais d'ophthalmologique 2013; 36(1): 50-4

Review Article

A review of the effectiveness of interdisciplinary services for the treatment of overweight and obese children in the community

Beatrice Farrugia, Charmaine Gauci

Abstract

The alarming rise in the prevalence of childhood obesity in recent years justifies an interest in evaluating the effectiveness of treatment interventions in the primary care setting, where they can be more accessible to the general population. This review aims to evaluate the effectiveness of multidisciplinary team interventions in this setting, in view of increasing recognition of the important role that such teams play in the treatment of childhood obesity.

A search of the Pubmed database was carried out based on pre-established inclusion and exclusion criteria. 26 studies from 18 different journals were included in the review, these being mainly behavioural, parenting and lifestyle interventions or combinations thereof. 18 of the studies reviewed reported on interventions that led to statistically significant changes in waist circumference, BMI or BMI-derived scores such as BMI percentiles and BMI z-scores. Assessing the clinical significance of the reported changes presented difficulties due to lack of explicit reporting of clinical significance and lack of widely-accepted weight-loss goals for such interventions in children.

The most successful interventions tended to feature standardized training of professional staff in the intervention and use of tailored educational material. While the exact formulation of the multidisciplinary team varied, the teams regularly feature professionals trained in the fields of nutrition, physical education/exercise therapy and psychology and often did not involve doctors beyond the participant referral stage. Low-intensity interventions where contact was made on a one-off, 3-6 monthly or monthly basis were generally ineffective.

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Introduction

The global prevalence of childhood overweight and obesity has increased at an alarming rate in the last quarter of a century, with an increase in the estimated number of affected children from 32 million in 1990[1] to 41 million in 2014[2]. The situation in Europe is no less concerning; one in three children aged from six to nine years participating in the second round of the Childhood Obesity Surveillance Initiative (COSI) were shown to be overweight or obese[3].

This situation has understandably resulted in a growing body of international research into prevention measures to prevent further increase in obesity rates and parallel interventions to achieve sustained weight loss and healthier lifestyles in children who are obese. Targeting these children is important as evidence shows that obese children have higher risk of carrying on obesity in adulthood[4]. Until recently, most paediatric obesity interventions took place in tertiary healthcare settings and research centres[5-6]. However, the importance of primary care-based obesity interventions is increasingly being recognised[7] and primary care is considered to have great potential as a setting for such interventions because it is more accessible to the population[5] and is widely used by children and their care-givers[8], with whom primary-

care providers often have a long-standing relationship.[6] For this reason, this review will focus on paediatric obesity interventions based in the primary care setting.

It is widely acknowledged that the multidisciplinary team has an important role to play in the treatment of childhood obesity[9-10]. Additionally, some research suggests that multidisciplinary interventions have the potential to offer more cost-effective care than previously reported interventions[11]. In view of this, this review includes interventions delivered by multidisciplinary teams.

Methodology

A search of the Pubmed database was carried out using the inclusion and exclusion criteria detailed in Table 1 and 2. Keywords used in the search were combined into groups defining each of the inclusion criteria, and the search was designed to retrieve articles with at least one term from each of these groups. Systematic reviews/meta-analyses were not included in the study but were reviewed for background information and assessed systematically to check if any references met the search criteria. The selection process for the review is described in the flowchart in Table 3. 25 studies were included in the final review.

***Table 1**: Inclusion criteria for the review*

Inclusion criteria:

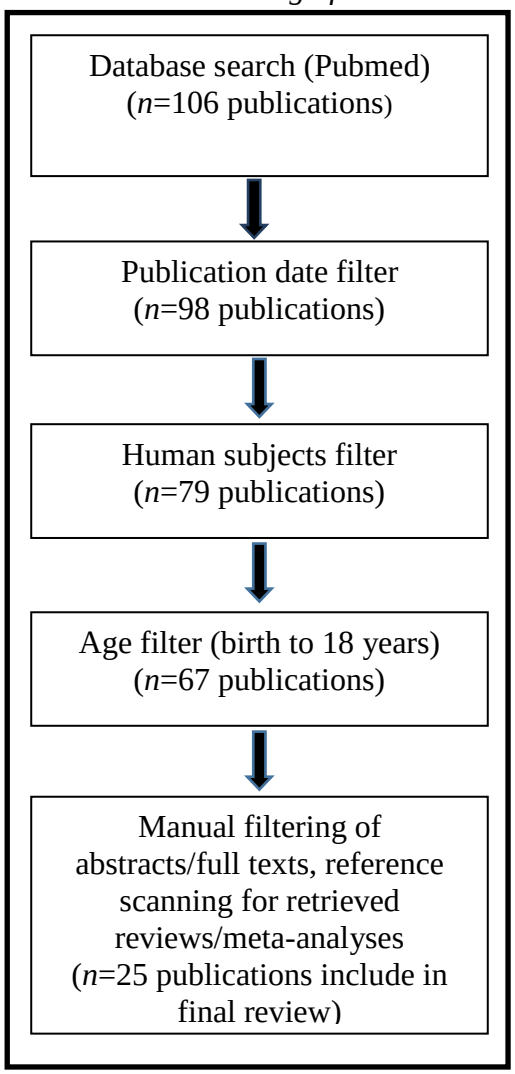
- studies must detail a randomised controlled trial or other intervention study for which results have been reported
- reported intervention must be an obesity/overweight treatment intervention aimed at children up to 18 years of age and/or their caregivers
- reported intervention must be wholly or mainly based in the primary care setting
- reported intervention must be interdisciplinary (involving more than one type of healthcare professional)

***Table 2**: Exclusion criteria for the review*

Exclusion criteria:

- study not available in English
- study published before 2000
- study involves surgical procedures as part of the treatment regime (surgical procedures were considered too specialised to be applicable to the primary care setting)

***Table 3**: Filtering of results*



Results

The review of literature in accordance with criteria included 25 studies from 18 different journals (table 1). The interventions included in this review are mainly behavioural, parenting and lifestyle interventions or combinations thereof, but one study involving pharmacological therapy.

Effectiveness of reviewed interventions

Of the 25 papers screened for this review, 7 of

them reported no significant effect on participants BMI or waist circumference[12–18]. While some studies reported that small sample size may have been the reason for failure to prove any significant effect[15] or that insufficient numbers of participants for reliable analyses to be possible[13], other studies failed to show body composition changes even when adequately powered to detect changes caused by as little as 0.5lbs of weight loss[12].

18 of the studies reviewed reported on interventions that led to statistically significant changes in waist circumference, BMI or BMI-derived scores such as BMI percentiles and BMI z-scores.

Clinical significance

Three of the studies specified in their results whether the changes in BMI achieved by study participants were clinically significant. In an RCT with parents as sole agents of change[19], 22% of previously overweight children in the intervention group were reclassified as having normal weight post-intervention while 8.7% of intervention group children previously classified as obese were reclassified as overweight. Another parent-focused intervention[20] led to 'clinically significant' reductions in BMI z-score at follow-up for one third of the intervention group while two-year follow-up of the 'Families for Health' intervention[21] reported clinically significant decreases in BMI z-score in 42% of participants.

Other studies reporting significant changes in primary outcomes did not explicitly report whether these were clinically significant. There are as yet no widely-accepted weight loss goals for such interventions in children.[22] The degree of weight lost by the child is strongly associated with the extent of improvement in their parameters for the risk factors making up the metabolic syndrome[23] which in turn is associated with increased risk of atherosclerosis and cardiovascular disease. The same study reported that while even minimal weight loss (BMI-SDS reduction of <0.25) resulted in improvement in glucose tolerance and blood pressure, reductions of >0.5 in BMI-SDS led to improvement in all metabolic syndrome parameters. By these criteria, assessing clinical significance of five of the remaining studies that reported weight loss results in BMI z-scores is relatively straightforward. Only one of the studies[24] reported a decrease in BMI z-score of > 0.5 and one other showed a mean decrease in BMI z-score in the intervention group of >0.25 (but <0.5)[25]. The remaining three studies reporting results in BMI z-scores showed modest results that do not denote clinically significant weight loss according to these criteria[26–28].

Assessing clinical significance of results for trials that reported weight changes in BMI percentile units[8,29] is more challenging; the highest and lowest percentiles lump together values that can differ widely and BMI percentiles lack the comparability across different ages, genders and anthropometric measures that BMI z-scores offer[30]. In fact, BMI percentile is not generally recommended for use as the analytic variable when change in adiposity is being investigated[31].

Yet other studies[32–34] reported only crude changes in BMI and weight. This makes it difficult to appreciate the significance of results as 'for BMI to be meaningful in children it must be compared to a reference-standard that accounts for child age and sex'[31]. One study[35] reported a reduction in BMI in 50% of intervention participants but did not specify the degree of this reduction, making it impossible to determine the level of effect.

Agent of change

The interventions included in this review varied in their main agent of change. The main agent of change was the participating adolescent in three interventions[28-29,36] and all reported statistically significant decreases in BMI z-score or weight circumference of their intervention groups. The evidence on the ideal extent of involvement of parents in weight control interventions for overweight adolescents is inconsistent[36] but many postulate that family-based models of care are less suited to adolescents as they gain autonomy and become less subject to parental influence[28]. On the other hand, some interventions where parents and children were shared agents of change involved a broad age-range with a mixture of child and adolescent participants[12,29,35,37] with varying success.

In the case of younger age groups, the need for parental involvement in weight loss interventions is generally acknowledged[38-39] and the majority of interventions reviewed involved parents and children as joint agents of change. Interestingly, in recent years it has been questioned whether children need to be involved at all in such

interventions[40].

Parents were sole agents of change in four reviewed interventions. Two of these[19-20] reported statistically significant improvements in primary outcomes compared to wait-list controls while the other two interventions failed to show any improvement in participants' body composition compared to their one-off information-giving and usual care control arms respectively.[16,18] Of note is the Project Story randomized control trial in which follow-up results showed statistically significant improvements in BMI z-scores for both the parent-only and family-based intervention arms compared to the wait-list controls but no significant difference between the results obtained for the two intervention groups.

Discussion

Any attempt to comment on the results of this review is made particularly challenging by the fact that a significant number of included studies are reported in a way that makes it difficult or impossible to assess the effectiveness and clinical significance of the intervention (as discussed in the section 'Clinical significance'). If this area of research is to prove as fruitful as possible it is important that a standard method of reporting weight loss outcomes in children is agreed upon to enable reliable comparisons between studies.

A closer look at included studies that proved ineffective for reasons other than lack of power[12,14,16–18] reveals no striking commonalities in their content. All but one did share a notable feature: they were low-intensity interventions where contact was made on a one-off, 3-6 monthly or monthly basis. On the other hand, the most effective interventions had moderate-to-high intensity contact with sessions weekly or twice-weekly for most of the duration of the intervention.

As regards logistics of the most successful interventions, notable features include standardized training of professional staff in the intervention and use of tailored educational material. In the case of the professions involved in the multidisciplinary team, while the exact formulation of team members varied, the teams regularly feature professionals trained in the fields of nutrition, physical education/exercise therapy and psychology and often did not involve doctors beyond the participant referral stage.

Further scrutiny of the reviewed studies with the most promising outcomes[11,20-21,24-25,41] reveals interesting patterns. Firstly, all the interventions placed an emphasis on skills transference and aimed to help parents and, in most cases, children to apply their knowledge in practice in their everyday lives. Another common feature was the encouragement of self-regulation, in the form of techniques such as self-monitoring, stimulus control and goal-setting. Interestingly, while self-regulation was encouraged, these interventions de-emphasised calorie-counting. The fact that the Traffic Light Diet features heavily among the most effective interventions is indicative of this general attitude; its simplicity and lack of emphasis on calorie-counting make it particularly suitable for use with children and encourages a focus on healthful nutrition choices.

Beyond simply focusing on encouraging healthy choices, the most successful interventions did not simply seek to encourage, but also to enable and facilitate healthier choices by drawing attention to ways in which parents could alter home environment and family dynamics to make them less obesogenic. This generally involved whole-of-family lifestyle changes that avoided 'othering' of the overweight child and extended intervention benefits beyond the participating child to their family members.

It is evident that for such environmental and lifestyle modifications to be sustained in the case of children who are not yet independent, parents of children with excess weight must be key figures. All of the most successful interventions gave importance to the role of parenting in the modification of children's weight-determining behaviours and attempted to provide parents with training in positive parenting practices such as parental modelling and reinforcement. This review unfortunately did not reveal any notable results from interventions targeting adolescents that would enable the authors to comment conclusively on the advisable level of involvement of parents and relative importance of parenting skills in the case of interventions targeting older children.

Limitations and biases

An important limitation of this study is the use of a single database. Searching other databases may have yielded more results and potentially led to different conclusions being drawn. Exclusion of studies unavailable in English is another potential source of bias.

This review was also limited by the inherent difficulty in making comparisons of effectiveness and clinical significance of results for interventions which reported their results using different weight outcome measures which were often not comparable. Furthermore, studies that met eligibility criteria displayed variety in intervention methodology and intensity, and there was no accepted standard for the types of healthcare professionals comprising multidisciplinary teams for paediatric obesity interventions.

Additionally, the extent to which generalizability of these results is advisable is influenced by the sample size of the individual interventions as well as the socio-cultural context interventions took place in. Issues of loss to follow-up and recruitment difficulties reported by several authors should be kept in mind. In a significant number of the included studies participants received incentives to participate. It is important to question whether certain interventions would be successful or sustainable without such incentives.

Conclusions

Among the articles reviewed, the most successful paediatric obesity interventions in the primary care setting tended to feature standardized training of professional staff in the intervention and use of tailored educational material with intervention participants. While the exact formulation of the multidisciplinary team varied, the teams regularly feature professionals trained in the fields of nutrition, physical education/exercise therapy and psychology. These interventions frequently did not involve doctors beyond the participant referral stage. Low-intensity interventions where contact was made with participants on a one-off, 3-6 monthly or monthly basis were generally ineffective.

The authors advocate the setting up of an intervention for the treatment of overweight and obese children in Malta. In light of the review findings, we recommend that such an intervention should incorporate a medium-to-high intensity, multi-disciplinary approach with input from nutritionists, psychologists and physical therapists, but it may also benefit from the involvement of other professionals. The emphasis of the intervention should be skills transference and self-regulation as this will empower both children and parents to enact and maintain lifestyle changes by fostering positive parenting practices, encouraging whole-of-family lifestyle change and addressing the obesogenic environment at the level of the family unit.

Bibliography

1. World Health Organisation. Global Strategy on Diet, Physical Activity and Health. 2002, (2014).
2. World Health Organisation. Report of the Commission on Ending Childhood Obesity. (2016).
3. Wijnhoven, T., Raaij, J. van & Breda, J. WHO European Childhood Obesity Surveillance Initiative. Implementation of round 1 (2007/2008) and round 2 (2009/2010). 1, (2014).
4. Deshmukh-Taskar, P. et al. Tracking of overweight status from childhood to young adulthood: the Bogalusa Heart Study. Eur. J. Clin. Nutr. 60, 48–57 (2006).
5. Sargent, G. M., Pilotto, L. S. & Baur, L. A. Components of primary care interventions to treat childhood overweight and obesity: A systematic review of effect. Obes. Rev. 12, 219–235 (2011).
6. Seburg, E. M., Olson-Bullis, B. A., Bredeson, D. M., Hayes, M. G. & Sherwood, N. E. A Review of Primary Care-Based Childhood Obesity Prevention and Treatment Interventions. Curr. Obes. Rep. 4, 157–173 (2015).
7. Wilfley, D. E., Kass, A. E. & Kolko, R. P. Counseling and behavior change in pediatric obesity. Pediatr. Clin. North Am. 58, 1403–1424 (2011).
8. RCT, M. I. and D. C. for O. in P. C. A. Motivational Interviewing and Dietary Counseling for Obesity in Primary Care: An RCT. Pediatrics 135, 649–657 (2015).
9. Hoey, H. Management of obesity in children differs from that of adults. Proc. Nutr. Soc. 73, 519–25 (2014).
10. Sample, D. A., Carroll, H. L., Barksdale, D. J. & Jessup, A. The Pediatric Obesity Initiative: development, implementation, and evaluation. J. Am. Assoc. Nurse Pract. 25, 481–487 (2013).
11. Hollinghurst, S., Hunt, L. P., Banks, J., Sharp, D. J. & Shield, J. P. Cost and effectiveness of treatment options for childhood obesity. Pediatr. Obes. 9, 26–34 (2014).
12. Gortmaker, S. L. et al. Evaluation of a primary care intervention on body mass index: the maine youth overweight collaborative. Child Obes 11, 187–193 (2015).
13. Hamilton-Shield, J. et al. Changing eating behaviours to treat childhood obesity in the community using Mandolean: The Community Mandolean randomised controlled trial (ComMando) - A pilot study. Health Technol. Assess. (Rockv). 18, 1–75 (2014).
14. Boudreau, A. D. A., Kurowski, D. S., Gonzalez, W. I., Dimond, M. A. & Oreskovic, N. M. Latino families, primary care, and childhood obesity: A randomized controlled trial. Am. J. Prev. Med. 44, S247–S257 (2013).

15. Davis, A. M. et al. The use of TeleMedicine in the Treatment of Pediatric Obesity: Feasibility and Acceptability. 7, 71–79 (2012).
16. Gerards, S. M. P. L. et al. The effectiveness of lifestyle triple P in the Netherlands: A randomized controlled trial. PLoS One 10, 1–18 (2015).
17. O'Connor, T. M., Hilmers, A., Watson, K., Baranowski, T. & Giardino, A. P. Feasibility of an obesity intervention for paediatric primary care targeting parenting and children: Helping HAND. Child. Care. Health Dev. 39, 141–149 (2013).
18. van Grieken, A. et al. Population-Based Childhood Overweight Prevention: Outcomes of the 'Be Active, Eat Right' Study. PLoS One 8, (2013).
19. Jansen, E., Mulkens, S. & Jansen, a. Tackling childhood overweight: treating parents exclusively is effective. Int. J. Obes. (Lond). 35, 501–509 (2011).
20. West, F., Sanders, M. R., Cleghorn, G. J. & Davies, P. S. W. Randomised clinical trial of a family-based lifestyle intervention for childhood obesity involving parents as the exclusive agents of change. Behav. Res. Ther. 48, 1170–1179 (2010).
21. Robertson, W., Thorogood, M., Inglis, N., Grainger, C. & Stewart-Brown, S. Two-year follow-up of the 'Families for Health' programme for the treatment of childhood obesity. Child. Care. Health Dev. 38, 229–236 (2012).
22. Kalavainen, M., Korppi, M. & Nuutinen, O. Long-term efficacy of group-based treatment for childhood obesity compared with routinely given individual counselling. Int. J. Obes. (Lond). 35, 530–533 (2011).
23. Reinehr, T., Kleber, M. & Toschke, A. M. Lifestyle intervention in obese children is associated with a decrease of the metabolic syndrome prevalence. Atherosclerosis 207, 174–180 (2009).
24. Goldfield, G. S., Epstein, L. H., Kilanowski, C. K., Paluch, R. a & Kogut-Bossler, B. Cost-effectiveness of group and mixed family-based treatment for childhood obesity. Int. J. Obes. Relat. Metab. Disord. 25, 1843–1849 (2001).
25. Sacher, P. M. et al. Randomized Controlled Trial of the MEND Program: A Family-based Community Intervention for Childhood Obesity. Obesity 18, S62–S68 (2010).
26. Janicke, D. M. et al. Comparison of parent-only vs family-based interventions for overweight children in underserved rural settings: outcomes from project STORY. Arch. Pediatr. Adolesc. Med. 162, 1119–1125 (2008).
27. Saelens, B. E. et al. Behavioral weight control for overweight adolescents initiated in primary care. Obes. Res. 10, 22–32 (2002).
28. DeBar, L. L. et al. A Primary Care-Based, Multicomponent Lifestyle Intervention for Overweight Adolescent Females. Pediatrics 129, e611–e620 (2012).
29. Duggins, M., Cherven, P., Carrithers, J., Messamore, J. & Harvey, A. Impact of family YMCA membership on childhood obesity: a randomized controlled effectiveness trial. J. Am. Board Fam. Med. 23, 323–333 (2010).
30. Nucara, A., Pietrafesa, M., Rizzo, G. & Scaccianoce, G. Handbook of Anthropometry. Handb. Anthr. 91–114 (2012). doi:10.1007/978-1-4419-1788-1
31. Must, A. & Anderson, S. PEDIATRIC MINI REVIEW Body mass index in children and adolescents: considerations for population-based applications. Int. J. Obes. 30, 590–594 (2006).
32. Barkin, S. L., Gesell, S. B., Po'e, E. K. & Ip, E. H. Changing overweight Latino preadolescent body mass index: the effect of the parent-child dyad. 73, 389–400 (2015).
33. Trial, A. R. C., Hampl, S., Jensen, C. & Boldrin, M. Effect of Orlistat on Weight and Body. Jama 293, 2873–2884 (2014).
34. Taveras, E. M. Randomized Controlled Trial to Improve Primary Care to Prevent and Manage Childhood Obesity. Arch. Pediatr. Adolesc. Med. 165, 714 (2011).
35. Banks, J., Sharp, D. J., Hunt, L. P. & Shield, J. P. H. Evaluating the transferability of a hospital-based childhood obesity clinic to primary care: A randomised controlled trial. Br. J. Gen. Pract. 62, 6–12 (2012).
36. Chanoine, J.-P., Hampl, S., Jensen, C., Boldrin, M. & Hauptman, J. Effect of Orlistat on Weight and Body. Jama 293, 2873–2884 (2014).
37. Anand, S. G., Adams, W. G. & Zuckerman, B. S. Specialized Care Of Overweight Children In Community Health Centers. Health Aff. 4, 712–717 (2016).
38. Spear, B. A. et al. Recommendations for treatment of child and adolescent overweight and obesity. Pediatrics 120 Suppl, S254-88 (2007).
39. Daniels, S. R. et al. Overweight in children and adolescents: Pathophysiology, consequences, prevention, and treatment. Circulation 111, 1999–2012 (2005).
40. Golan, M., Kaufman, V. & Shahar, D. Childhood obesity treatment: targeting parents exclusively v. parents and children. Br. J. Nutr. 95, 1008–1015 (2006).
41. Rito, A. I., Carvalho, M. A., Ramos, C. & Breda, J. Program Obesity Zero (POZ)--a community-based intervention to address overweight primary-school children from five Portuguese municipalities. Public Health Nutr. 16, 1043–51 (2013).

Review Article

Folic Acid – Recommendations and Interventions

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Introduction

Folic acid (FA) is known to play an important role in the prevention of birth defects.[1] Neural tube defects (NTDs) are severe congenital anomalies many of which are considered potentially preventable if mothers take adequate folic acid in the peri-conceptional period i.e. from at least one month before to one month after conception. Folates are required for the normal development and closure of the neural tube in the early stages of embryonic development (neurulation stage embryos). The exact pathogenic mechanisms underlying NTD development are complex and remain to be elucidated.[2-3]

NTDs are reported to occur at an overall prevalence rate of 10.29 per 10,000 births (2011-2015) in European countries.[4] It has been estimated that the lowest achievable rate of non-preventable NTD with folic acid is 5-6 per 10,000 births,[5] hence European countries can potentially half the current occurrence of NTDs if women were to take adequate folic acid in the peri-conception period.

Women's peri-conceptional blood folate levels may be augmented in three main ways: by increasing food folate intake, through FA vitamin supplementation and by fortification of food with folic acid.[6]

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Studies have shown that encouraging increased food folate intake alone is often inadequate to reach the optimal levels required to effectively decrease the incidence of NTDs.[7-8] It has been estimated that to consume the recommended amount of food folate, a person would need to eat an unrealistic quantity of certain food such as: "*23 spears of cooked asparagus or 4 cups of cooked okra or 4 cups of raw spinach or 2 slides of beef liver or 6 cups of orange juice or 4.5 cups of cooked broccoli*.[9] In view of this Health Authorities around the globe have embarked on further public health initiatives directed at improving women's peri-conceptional folate status, these include the issuing of National Guidelines and Recommendations, Health Promotion Campaigns and Mandatory Food Fortification with FA.[10-11]

This review describes the public health recommendations and interventions that have been undertaken in a bid to increase women's preconception folic acid intake and the successes, or otherwise, of the various actions.

National Guidelines and Recommendations

In 1992, both the US and Britain issued recommendations advising women planning pregnancy to take FA supplementation.[12-13] These were followed by similar recommendations in 1993 in a number of countries including Canada, New Zealand, China, South Africa, Ireland, Spain, Norway and the Netherlands.[11] Since then several other countries have issued policies and recommendations related to increasing folate intake and peri-conceptional FA supplementation.[10]

In January 1992, a UK Department of Health Expert Advisory Group released recommendations that all women planning a pregnancy should take 400ug of FA supplement per day and women with a history of NTD should take 4mg of FA preconceptionally and through the first 12 weeks of pregnancy.[13] These recommendations still hold today, with the latest position statement of the Scientific Advisory Committee on Nutrition

(SACN) recommending that even if food fortification is introduced, *"all women who could become pregnant and those with a history of a previous NTD-affected pregnancy should continue to supplement their diet with 400 µg and 5 mg per day of folic acid respectively prior to conception and until the twelfth week of pregnancy"* (Article 17).[14]

Similarly, US guidelines[12] issued in September 1992 advised that "*all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs*". The guidelines continue to state that "*women who have had a prior NTD-affected pregnancy are at high risk of having a subsequent affected pregnancy. When these women are planning to become pregnant, they should consult their physicians for advice.*"[12] as higher doses of FA are merited in such circumstances.

It is recommended that for optimal prevention of NTDs, FA supplementation is to be taken from at least one month prior to conception, as neural tube development starts in the very early embryological stages of development, and should be continued through the first trimester of pregnancy .[15] Such use is reflected in the official policies released by the various countries.

In spite of national recommendations being in place research has shown that women's compliance with FA supplementation remains inadequate,[16-17] indicating that more than just guidelines are needed.

Health Promotion campaigns

Subsequent to national recommendations and guidelines, a number of national and regional health promotion campaigns were developed and aimed at actively increasing women's awareness and knowledge of the benefits of FA and the recommendations for uptake of FA supplementation. The rationale of these campaigns is that greater awareness and knowledge of the association between the correct use of FA and prevention of NTDs would result in improved uptake of FA supplementation in women, with consequent increase in their blood folate levels and decrease in the occurrence of NTDs.[18]

Research has shown that whereas health promotion campaigns can and do significantly increase women's awareness and knowledge of FA supplementation, correct peri-conceptual use does not increase to such an extent, with the observed increase in the rates of preconception supplementation remaining far less than desired.[19] These low rates of preconception supplementation persist even when pregnancy has been planned.[20] More importantly, follow up studies show that the decrease in occurrence of NTDs following such campaigns has not been satisfactory, even in countries where voluntary food fortification is available.[17]

Most studies evaluating the effectiveness of Health Promotion Campaigns conclude that whereas campaigns have been effective in increasing women's awareness and knowledge, there have been disappointing results regarding their effectiveness in increasing preconception consumption of FA.[21]

Chivu *et al* (2007)[22] conducted a systematic literature review identifying studies reporting on the results of health promotion interventions carried out to "*increase awareness, knowledge and folic acid consumption before and during pregnancy*". The authors identified a total of 31 studies meeting their inclusion criteria and they found that "*on average, women's awareness increased from 60% to 72%, knowledge from 21% to 45% and consumption from 14% to 23%"* concluding that in spite of increased awareness women's *"average usage was less than 25%"*.[22] These results were further corroborated by another comprehensive systematic review of the literature conducted by Rofail *et al*[23] in 2012, who conclude that "*these campaigns usually changed the knowledge and behaviour of less than half the target population"* (p.95).[23]

Table 1 gives a summary of the findings of studies, published since 2010, investigating and documenting women's peri-conception FA supplementation.

Table 1: *Women's pre / peri-conception folic acid supplementation*

Country	Authors	Year Published	Study Population / sample	Survey dates	Sample size	Peri-conception use of FA *(%)*
EUROPE						
Denmark	Rasmussen and Clemmensen[44]	2010	Consecutive pregnant women attending a midwife consultation.	Aug 2008	84	*51.2*
Ireland	Delany *et al*[45]	2011	Women attending first antenatal visit at three maternity hospitals in Dublin.	Jul-Sep 2009	297	*36.0**
Netherlands	Zetstra-van der Woude *et al*[46]	2012	Pregnant women attending antenatal visits. Survey carried out in the Northern Netherlands**.**	2009	515	*51.6**
France	Tort *et al*[47]	2013	Nationally representative sample of women giving birth in France	2010	12646	*14.8*
Italy	Lauria *et al*[48]	2014	Sample surveys of delivering women from 3 birthing centres in Italy	2010-12	973	*37.9*
USA and CANADA						
Canada-National	Miller *et al*[49]	2011	Stratified random selection of post-partum women identified through the Canadian Census of Population as having delivered in the three-month period preceding the 2006 Census. Part of Canadian Maternity Experiences Survey.	2006	6421	*57.7*
USA	Hoyo *et al* [50]	2011	Pre-pregnancy & pregnancy-related data on dietary supplementation obtained by interviewing pregnant women at two obstetric-care facilities in Durham County, North Carolina.	2005-08	539	*51*
MIDDLE EAST						
UAE	Al-Hossani *et al*[51]	2010	Pregnant women of UAE nationality in Abu Dhabi Emirate attending 2 main maternal and child health centres.	Not given	277	7.8
Iran	Nosrat *et al*[52]	2012	Convenience purposive sampling of primaparous women registered with Primary Health Care Centres, private gynaecology clinic and the Dezyani Gynaecology and Obstetrics hospital.	Jun-Nov 2008	676	2.0
ASIA						
China	Zeng *et al*[53]	2011	Women attending prenatal or pre-pregnancy care visits in six provinces in Northern China.	Jun-Aug 2008	33025	*8.0**
	Xing *et al*[54]	2012	Pregnant women attending routine antenatal care for the first time in regions of Hefei and Maanshan. Study carried out within the China Anhui Birth Defects and Child Development Cohort study.	Oct 08 – Sep 09	4290	*16.1**
Taiwan	Jou *et al*[55]	2010	Women attending a community hospital in North Taiwan for their first antenatal visit.	Mar–Dec 2008	275	*15.6*
AUSTRALIA						
New South Wales	Wilton and Foureur[56]	2010	Consecutive primagravidae women attending antenatal clinic of a tertiary hospital in Sydney.	Sept 05-Mar 06	295	*23.4**

* Reported percentage stated specifically to include the use of FA at least 4 weeks before until at least 4 weeks after conception. Unmarked rates are those described as 'prenatal' and/or 'perinatal' consumption but full period of FA use not specified.

Health Promotion Campaigns and NTDs

Issuing recommendations and undertaking health promotion campaigns to increase women's peri-conceptional FA knowledge and uptake without reaching the primary intended goal of reducing NTDs could be considered futile. Disappointingly, it has been shown that in spite of extensive health promotion campaigns, the decrease in occurrence of NTDs has not been satisfactory,[24] with several studies reporting only a mild and often insignificant decrease in reduction in NTDs after introducing recommendations and FA campaigns without implementing mandatory food FA fortification.[25-26]

This limited success in reducing potentially preventable NTDs through health promotion campaigns is described in a comprehensive review by Botto *et al* (2005)[17] who investigated the occurrence of NTDs using data from 13 birth registries in Europe that could report on NTD prevalence before and after the issuing of recommendations. The authors found that "*rates of neural tube defects showed no detectable change.... regardless of the recommendations' form, timing, and intended target"* (p.574-575).[17]

A more recent paper by Khoshnood *et al* (2015)[27] highlights that this situation persists and '*recommendations, voluntary fortification, or both have not been effective in decreasing the prevalence of neural tube defects in Europe'*. This contrasts with the decrease of neural tube defects seen in other countries that have introduced mandatory fortification. The authors emphasize that '*voluntary guidance for women isn't working and Europe should seriously consider mandatory fortification'* (p.5).[27]

These findings clearly indicate that more than just recommendations and health promotion campaigns are necessary to achieve the desired prevention of avoidable NTDs.

Mandatory Food Fortification

Confronted with the widely documented limited success of the recommendations and health promotion initiatives to increase women's peri-conceptional uptake of FA to decrease the occurrence of NTDs, researchers have argued that new approaches are needed.[28] Indeed, several prominent public health officials and epidemiologists have advocated strongly in favour of mandatory, widespread staple food (grain) fortification with FA.[29-30]

Concerns regarding the health risks of the widespread use of FA food fortification and the issue of freedom of choice have hindered the implementation of FA food fortification especially in Europe.[31]

The main health concerns related to mandatory food fortification with FA include possible masking of Vitamin B12 deficiency, associations with certain cancers, cognitive decline and autism. However, current research is inconclusive and none of these concerns have been confirmed at the recommended levels of food fortification. The evidence is generally deemed insufficient to impede the consideration of food fortification to decrease NTDs. Further discussion of these health concerns can be found elsewhere.[32-38]

Table 2: *Countries that have introduced mandatory fortification*

Country	Year of implementation of Mandatory Fortification	Level of fortification mandated
USA*	1998	140 µg /100g flour
Canada*	1998	150 µg /100g flour
Costa Rica*	1998	180 µg/100g flour
Chile*	2000	220 µg/100g flour
South Africa*	2003	150 ug/100g flour
Brazil**	2004	150 µg /100g flour
Australia***	2009	2-3 mg/kg flour

*Crider et al, 2011[57]; **Pacheco, 2009[58]; ***FSANZ, 2009[59]

Table 3: *NTD rates pre and post mandatory food fortification (listed by year of fortification)*

Country By Year of mandatory folic acid fortification introduced and level of fortification mandated	Conditions reported	Pre-fortification NTD rate/1,000 (Reference time period)	Post-fortification NTD rate/1000 (Reference time period)	Decline in NTD rate *(%)*
Oman (1996 – 5mg/kg flour)				
(Alasfoor *et al*, 2010)[60]	Spina bifida	**3.06**** (1996)	**2.11** (1997)	***31%***
Canada (1998 - 150ug/100g flour)				
7 Canadian Provinces (De Wals *et al*, 2007)[61]	All NTDs	**1.58*** (1993-1997)	**0.86*** (2000-2002)	***46%***
Newfoundland (Liu *et al*, 2004)[62]	All NTDs	**4.36*** (1991-97)	**0.96*** (1998-01)	***78%***
Nova Scotia (Persad *et al*, 2002)[63]	All NTDS	**2.58*** (1991-97)	**1.17*** (1998-00)	***55%***
Ontario (Ray *et al*, 2002)[64]	Anencephaly and Spina bifida	**1.13*** (Jan 94-Dec 97)	**0.58*** (Jan 98-Mar 00)	***49%***
USA (1998 - 140ug/100g flour)			**-**	**-**
US, California (Chen *et al*, 2008)[65]	Anencephaly and Spina bifida	**0.85**** (1986-96)	**0.72**** (1998-03)	***15%***
US, 8 States (Canfield *et al*, 2005)[66]	Anencephaly	**0.42*** (1995-96)	**0.35*** (1999-00)	***17%***
	Spina Bifida	**0.64*** (1995-96)	**0.41*** (1999-00)	***36%***
United States, CDC (Honein *et al*, 2001)[67]	Anencephaly and Spina bifida	**0.38**** (Oct 95-Dec 96)	**0.31**** (Oct 98-Dec 99)	***19%***
Costa Rica (1998 - 180ug/100g flour)				
(Tascan-Chen *et al*, 2004)[68]	All NTDs	**9.7**** (1996-98)	**6.3**** (1999-00)	***35%***
(Maria Paz Barboza *et al*, 2015)[69]	All NTDs	9.8 (1996-1998)	4.8 (2003-2012)	***51%***
Chile (2000 - 220ug/100g flour)				
(Cortes *et al*, 2012)[70]	All NTDs	**1.71** (1999-2000)	**0.86** (2001-2009)	***51%***
Saudi Arabia (2001 – 1.6mg/kg flour)				
(Safdar *et al*, 2007)[71]	All NTDs	**1.9**** (1997-00)	**0.76**** (2001-2005)	***60%***
Jordan (2002 – 1.5ppm in flour)				
(Amarin *et al*, 2010)[72]	All NTDs	**1.85*** (2000-01)	**0.95*** (2005-06)	***49%***
South Africa (2003 – 1.5mg/kg flour)				
(Sayed *et al*, 2008)[73]	All NTDs	**1.41**** (Jan 03- Jun 04)	**0.98**** (Oct 04 – Jun 05)	***31%***
North Iran (2007 – 150ug/100g flour)				
(Golalipour *et al*, 2014)[74]	All NTDs	**1.78*** (Mar 06- Jun 07)	**0.84*** (Mar 08 – Sep 09)	***53%***
Australia (2009 – 2-3mg/kg flour)				
(Bower *et al*, 2016)[75]	All NTDs	**2.43*** (2007- 2009)	**0.82*** (2010-2014)	***66%***

Implementation of food fortification

Over 50 countries globally have introduced mandatory fortification of grain products with folic acid.[39] Table 2 lists a few of the countries that have introduced fortification and the levels of food fortification they have implemented.

In Europe, although several national recommendations and health promotion campaigns have been undertaken, mandatory food fortification remains unimplemented and, to date, European women rely on peri-conceptional supplementation and voluntary fortification of certain foods. This has been criticised widely as a "*Missed Opportunity*" in introducing effective public health intervention for the primary prevention of severe birth defects.[26]

In 2007, the UK Food Standards Agency (FSA) recommended the *"mandatory fortification of white and brown wheat flour"* (p.19)[40] however, this has not yet been implemented.

Food fortification and NTDs

In countries that have introduced food fortification, red blood cell folate and serum folate levels in the general population have been found to increase, while elevated homocysteine levels, associated with increased risk of cardiovascular disease, have decreased.[41]

Studies have been undertaken in countries that have implemented FA food fortification to evaluate the occurrence of NTDs before and after fortification.[42] These studies, from different regions around the world, report a significant reduction in NTDs immediately following mandatory food fortification. Table 3 gives a summary of studies presenting pre and post-mandatory food fortification and neural tube defect prevalence. The significant decrease in NTDs experienced is unequivocal.

A recent meta-analysis of the global prevalence of spina bifida by folic acid fortification status gives the overall rate of neural tube defects for livebirths, stillbirths and terminations of pregnancy in countries with fortification as 35.22/100,000 births (95% CI 32.18-38.56) while this rate is 52.29/100,000 (95% CI 46.28-59.08) in countries that have not implemented mandatory fortification.[43]

Mandatory food fortification with FA has thus been shown to have effectively reached the primary aim of decreasing the occurrence of potentially preventable NTDs in several diverse countries.

Conclusions

The public health interventions implemented to improve maternal peri-conceptional FA intake vary from minimal recommendations to official policies and health education campaigns through to legislation with mandatory fortification of staple foods. The wide variation in degree of intervention implemented reveals the fact that there is no consensus on the ideal level of public health intervention as regards FA supplementation and food fortification and just how far the state should intervene is controversial.[30,36]

Many countries worldwide have issued official recommendations often accompanied by extensive and expensive health promotion campaigns encouraging women's preconceptional intake of folic acid; these have, however, had limited benefits in the decrease of occurrence of NTDs. This contrasts with the evidence of success in countries that have implemented mandatory food fortification with folic acid.

The policy maker's decision to undertake the implementation or otherwise of any intervention is not to be taken lightly and must be based on well informed, evidence based assessments. Taking no action is also associated with its consequences - those of failing to prevent potentially avoidable major birth defects.

References:

1. Gatt M, Muscat Baron Y, Lautier EC, Calleja N. Folic acid and prevention of birth defects. Malta Med J. 2016;28(4):49-54.
2. Copp AJ, Stanier P, Greene NDE. Europe PMC Funders Group Neural tube defects – recent advances , unsolved questions and controversies. Lancet Neurolo. 2013;12(8):799-810.
3. Imbard A, Benoist JF, Blom HJ. Neural Tube Defects, Folic Acid and Methylation. Int J Environ Res Public Heal. 2013;10(9):4352-4389.
4. EUROCAT. Prevalence Tables. European Surveillance of Congenital Anomalies. http://www.eurocat-network.eu/accessprevalencedata/prevalencetables. Published 2016. Accessed June 6, 2017.
5. Crider KS, Devine O, Hao L, Dowling NF, Zhu J, Berry RJ. Population red blood cell folate concentrations for prevention of neural tube defects : bayesian model. BMJ. 2014;4554(July):1-12.
6. Werler MM, Louik C, Mitchell AA. Achieving a public health recommendation for preventing neural tube defects with Folic Acid. Am J Public Heal. 1999;89:1637-40.

7. Cena ER, Joy AB, Heneman K, et al. Folate Intake and Food-Related Behaviors in Nonpregnant, Low-Income Women of Childbearing Age. J Am Diet Assoc. 2008;108(8):1364-8.
8. Elkin AC, Higham J. Folic acid supplements are more effective than increased dietary folate intake in elevating serum folate levels. BJOG An Int J Obstet Gynaecol. 2000;107(2):285-9.
9. Food Fortification Initiative. http://www.ffinetwork.org/why_fortify/PreventNTDs.html). Published 2017.
10. Eurocat Folic Acid Working Group. Special Report: Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe. 2009;44(December). http://www.eurocat-network.eu/content/Special-Report-NTD-3rdEd-Part-I.pdf.
11. Cornel MC, Erickson JD. Comparison of national policies on periconceptional use of folic acid to prevent spina bifida and anencephaly (SBA). Teratology. 1997;55(2):134-7.
12. CDC (Center for Disease Control). Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR. 1992;41(RR-14):1-7.
13. Department of Health. Report from an Expert Advisory Group (1992) on Folic Acid and the Prevention of Neural Tube Defects.; 1992.
14. SACN Scientific Advisory Committee on Nutrition. Folic Acid and Colorectal Cancer Risk: Review of recommendation for mandatory folic acid fortification. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/339293/SACN_Report_to_CMO_on_folic_acid_and_colorectal_cancer_risk_.pdf. Published 2009.
15. World Health Organisation. Prevention of Neural Tube Defects. Standards for Maternal and Neonatal care.
16. CDC, Centers for Disease Control and Prevention. Use of supplements containing folic acid among women of childbearing age--United States, 2007. MMWR, 2008; 57(1), 5-8.
17. Botto LD, Lisi A, Robert-Gnansia E, et al. International retrospective cohort study of neural tube defects in relation to folic acid recommendations: are the recommendations working? Br Med J. 2005;330(7491):571-3.
18. Ren A, Zhang L, Li Z, Hao L, Tian Y, Li Z. Awareness and use of folic acid, and blood folate concentrations among pregnant women in northern China-An area with a high prevalence of neural tube defects. Reprod Toxicol. 2006;22(3):431-6.
19. De Walle HEK, De Jong-Van Den Berg LTW. Ten years after the Dutch public health campaign on folic acid: The continuing challenge. Eur J Clin Pharmacol. 2008;64(5):539-43.
20. De Santis M, Quattrocchi T, Mappa I, et al. Folic acid use in planned pregnancy: An Italian survey. Matern Child Health J. 2013;17(4):661-6.
21. van der Pal-de Bruin KM, de Walle HE, Jeeninga W, et al. The Dutch "Folic Acid Campaign"--have the goals been achieved? Paediatr Perinat Epidemiol. 2000;14(2):111-117.
22. Chivu CM, Tulchinsky TH, Soares-Weiser K, Braunstein R, Brezis M. A systematic review of interventions to increase awareness, knowledge, and folic acid consumption before and during pregnancy. Am J Health Promot. 2007;22(4):237-45.
23. Rofail D, Colligs A, Abetz L, Lindemann M, Maguire L. Factors contributing to the success of folic acid public health campaigns. J Public Health (Bangkok). 2012;34(1):90-9.
24. du Plessis L, Hunt RW, Fletcher AS, Riley MM, Halliday JL. What has happened with neural tube defects and women's understanding of folate in Victoria since 1998? Med J Aust. 2008;189(10):570-4.
25. Clemmensen D, Thygesen M, Rasmussen MM, Fenger-Gr??n M, Petersen OB, Mosdal C. Decreased incidence of myelomeningocele at birth: Effect of folic acid recommendations or prenatal diagnostics? Child's Nerv Syst. 2011;27(11):1951-5.
26. Busby A, Armstrong B, Dolk H, et al. Preventing neural tube defects in Europe: A missed opportunity. Reprod Toxicol. 2005;20(3).
27. Khoshnood B, Loane M, De Walle H, et al. Long term trends in prevalence of neural tube defects in Europe: Population based study. BMJ. 2015;351(h5949):1-6.
28. Coll O, Palacio M. Prevention of NTDs: New strategies are needed. Am J Obstet Gynecol. 2006;194(6):1740.
29. Dolk H, Abramsky L. Should Europe fortify a staple food with folic acid? Lancet. 2007;369:641-2.
30. Wald NJ, Oakley GP. Should folic acid fortification be mandatory? Yes. BMJ Br Med J. 2007;334(7606):1252.
31. Eichholzer M, Tönz O, Zimmermann R. Folic acid: a public-health challenge. Lancet. 2006;367(9519):1352-61.
32. Jägerstad M. Folic acid fortification prevents neural tube defects and may also reduce cancer risks. Acta Paediatr. 2012;101(10):1007-12.
33. Wien TN, Pike E, Wisløff T, Staff A, Smeland S, Klemp M. Cancer risk with folic acid supplements: a systematic review and meta-analysis. BMJ Open. 2012;2(1):e000653.
34. Berry RJ, Bailey L, Mulinare J, Bower C, Dary O. Fortification of flour with folic acid. 2010;31(1):22-35.
35. Johnston RB. Will increasing folic acid in fortified grain products further reduce neural tube defects without causing harm? Consideration of the evidence. Pediatr Res. 2008;63(1):2-8.
36. Hubner RA, Houlston RD, Muir KR. Should Folic Acid fortification be mandaory? No. BMJ Br Med J. 2007;334:1253.
37. Mason JB, Dickstein A, Jacques PF, et al. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: A hypothesis. Cancer Epidemiol Biomarkers Prev. 2007;16(7):1325-9.

38. Cole BF, Baron JA, Sandler RS, et al. " Folic Acid for the prevention of colorectal adenomas ." JAMA. 2007;297(21):2351-59.
39. Food Fortification Initiative. Enhancing grains for healthier life. http://www.ffinetwork.org. Published 2016.
40. Food Standards Agency. Folic Acid Fortification. http://www.food.gov.uk/. Published 2007.
41. Rader JI. Diet , DNA Methylation Processes and Health Folic Acid Fortification , Folate Status and Plasma Homocysteine 1. J Nutr. 2002;(5):2466-2470.
42. Castillo-Lancellotti C, Tur J a, Uauy R. Impact of folic acid fortification of flour on neural tube defects: a systematic review. Public Health Nutr. 2012;16(July):1-11.
43. Atta CAM, Fiest KM, Frolkis AD, et al. Global birth prevalence of spina bifida by folic acid fortification status: A systematic review and meta-analysis. Am J Public Health. 2016;106(1):e24-e34.
44. Rasmussen MM, Clemmensen D. Folic acid supplementation in pregnant women. Dan Med Bull. 2010;57(1):A4134. http://www.ncbi.nlm.nih.gov/pubmed/20175948.
45. Delany c, McDonnell R, Robson M, Corcoran S, Fitzpatrick C DLHD. Folic acid supplement use in the prevention of Neural Tube Defects in 2009. Ir Med J. 2011;104(September):12-15.
46. Zetstra-van der Woude PA, de Walle HEK, de Jong-van den Berg LTW. Periconceptional folic acid use: Still room to improve. Birth Defects Res Part A - Clin Mol Teratol. 2012;94(2):96-101.
47. Tort J, Lelong N, Prunet C, Khoshnood B, Blondel B. Maternal and health care determinants of preconceptional use of folic acid supplementation in France: Results from the 2010 National Perinatal Survey. BJOG An Int J Obstet Gynaecol. 2013;120(13):1661-7.
48. Lauria L, Adinolfi G, Bartolomeo F, Petruccelli E, Grandolofo M. Women ' s knowledge and periconceptional use of folic acid : data from three birth centers in. Int J Public Heal Public Heal. 2014;1(1):99-107.
49. Miller EC, Liu N, Wen SW, Walker M. Why Do Canadian Women Fail to Achieve Optimal Pre-Conceptional Folic Acid Supplementation? An Observational Study. J Obstet Gynaecol Canada. 2011;33(11):1116-23.
50. Hoyo C, Murtha AP, Schildkraut JM, et al. Folic acid supplementation before and during pregnancy in the Newborn Epigenetics STudy (NEST). BMC Public Health. 2011;11(1):46.
51. Al-Hossani H, Abouzeid H, Salah MM, Farag HM, Fawzy E. Knowledge and practices of pregnant women about folic acid in pregnancy in Abu Dhabi, United Arab Emirates. East Mediterr Heal J. 2010;16(4):402-407. http://www.ncbi.nlm.nih.gov/pubmed/20795424.
52. Nosrat SB, Sedehi M, Golalipour MJ. Knowledge and practice of urban Iranian pregnant women towards folic acid intake for neural tube defect prevention. J Pak Med Assoc. 2012;62(8):785-9.
53. Zeng Z, Yuan P, Wang Y, Ma X, Zhu J. Folic acid awareness and intake among women in areas with high prevalence of neural tube defects in China: a cross-sectional study. Public Health Nutr. 2011;14(7):1142-7.
54. Xing XY, Tao FB, Hao JH, et al. Periconceptional folic acid supplementation among women attending antenatal clinic in Anhui, China: Data from a population-based cohort study. Midwifery. 2012;28(3):291-7.
55. Jou HJ, Hsu IP, Liu CY, Chung SH, Chen SM, Gau ML. Awareness and Use of Folic Acid Among Pregnant Women in Taipei. Taiwan J Obstet Gynecol. 2010;49(3):306-10.
56. Wilton DC, Foureur MJ. A survey of folic acid use in primigravid women. Women and Birth. 2010;23(2):67-73.
57. Crider KS, Bailey LB, Berry RJ. Folic acid food fortification-its history, effect, concerns, and future directions. Nutrients. 2011;3(3):370-84.
58. Pacheco SS, Braga C, Souza AI de, Figueiroa JN. Effects of folic acid fortification on the prevalence of neural tube defects. Rev Saude Publica. 2009;43(4):565-71.
59. Food Standards Australia New Zealand. Australian User Guide Mandatory Folic Acid Fortification. 2009;(February):10-18.
60. Alasfoor D, Elsayed MK, Mohammed A. Spina bifida and birth outcome before and after fortification of flour with iron and folic acid in Oman. East Mediterr Heal J. 2010;16(5):533-8.
61. De Wals P, Tairou F, Van Allen MI, et al. Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med. 2007;357(2):135-142.
62. Liu S, West R, Randell E, et al. A comprehensive evaluation of food fortification with folic acid for the primary prevention of neural tube defects. BMC Pregnancy Childbirth. 2004;4(1):20.
63. Persad VL, Van den Hof MC, Dubé JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. CMAJ. 2002;167(3):241-5. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=117468&tool=pmcentrez&rendertype=abstract.
64. Ray JG, Meier C, Vermeulen MJ, Boss S, Wyatt PR, Cole DEC. Association of neural tube defects and folic acid food fortification in Canada. Lancet. 2002;360(9350):2047-8.
65. Chen BH, Carmichael SL, Selvin S, Abrams B, Shaw GM. NTD prevalences in central California before and after folic acid fortification. Birth Defects Res Part A - Clin Mol Teratol. 2008;82(8):547-52.
66. Canfield MA, Collins JS, Botto LD, et al. Changes in the birth prevalence of selected birth defects after grain fortification with folic acid in the United States: Findings from a multi-state population-based study. Birth Defects Res Part A - Clin Mol Teratol. 2005;73(10):679-89.
67. Honein MA, Paulozzi LJ, Mathews TJ, et al. Impact of Folic Acid Fortification of the US Food Supply on the Occurrence of Neural Tube Defects. Jama. 2001;285(23):2981.

68. Tacsan-Chen L, Rivera A. The Costa Rican experience: reduction of neural tube defects following food fortification programs. Nutr Rev. 2004;62(6):S40-S43.
69. María de la Paz Barboza-Arguello, Lila M. Umaña-Solis, Alejandro Azofeifa, Diana Valencia, Alina L. Flores, Sara Ridríguez-Aguilar, Thelma Alfaro-Calvo JM. Neural Tube Defects in Costa Rica, 1987–2012: Origins and Development of Birth Defect Surveillance and Folic Acid Fortification. Matern Child Heal J. 2015;19 (3):583-90.
70. Cortes F, Mellado C, Pardo RA, Villarroel LA, Hertrampf E. Wheat flour fortification with folic acid: Changes in neural tube defects rates in Chile. Am J Med Genet Part A. 2012;158 A(8):1885-90.
71. Safdar OY, Al-Dabbagh AA, AbuElieneen WA, Kari JA. Decline in the incidence of neural tube defects after the national fortification of flour (1997-2005). Saudi Med J. 2007;28(8):1227-29.
72. Amarin ZO, Obeidat AZ. Effect of folic acid fortification on the incidence of neural tube defects. Paediatr Perinat Epidemiol. 2010;24(4):349-51.
73. Sayed AR, Bourne D, Pattinson R, Nixon J, Henderson B. Decline in the prevalence of neural tube defects following folic acid fortification and its cost-benefit in South Africa. Birth Defects Res Part A - Clin Mol Teratol. 2008;82(4):211-6.
74. Golalipour MJ, Arabi M, Ali Vakili M. Impact of flour fortification with folic acid on the prevalence of neural tube defects in Northern Iran. J Pediatr Neurol. 2014;12(2):69-73.
75. Bower C, Maxwell S, Hickling S, D'Antoine H, O'Leary P. Folate status in Aboriginal people before and after mandatory fortification of flour for bread-making in Australia. Aust New Zeal J Obstet Gynaecol. 2016;56(3):233-7.

Trans-oral Resection of Nasopharyngeal Pleomorphic Adenoma, a Case Report

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Abstract

Introduction: Around 80% of all salivary gland tumours are pleomorphic adenomas, most commonly found in the parotid gland. This case report regards the rare finding of a pleomorphic adenoma in the nasopharynx.

Case Presentation: a 29 year old lady presented to the ENT department with a 4 month history of worsesning and non-resolving nasal obstruction, change in voice, snoring and right aural congestion. A smooth mass pushing the uvula forward was seen on oral examination, and flexible nasoendoscopy revealed an exophytic mass from the right nasopharynx. CT and MRI showed a non-erosive mass in the right nasopharynx. Incisional biopsy was carried out which showed features of pleomorphic adenoma. Lesion was excised using transoral technique to remove the tumour with an intact capsule.

Literature Review and Discussion: A PubMed search found only 12 previously reported cases of pleomorphic adenoma from 1970 to 2015. The treatment of choice was surgical in all cases, one case reports the use of radiotherapy, without affect. The trans-oral technique used in this case ensured that the tumour was removed with the surrounding capsule intact, thus reducing risk of recurrence.

Conclusion: This is the first reported case of nasopharyngeal pleomorphic adenoma from Malta. Diagnosis was made by the triple assessment – examination, radiology and histology. The tumour was excised completely and the plan is for the patient to have regular follow up.

Keywords

Nasopharynx; nasopharyngeal; pleomorphic; adenoma

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Introduction

Pleomorphic adenomas are the most common salivary gland tumours, making up 70-80% % of all salivary gland neoplasms. These are most commonly found in the parotid glands.
Presentation of a pleomorphic adenoma in the nasopharynx is a very rare occurrence.

Case Presentation

A 29 year old female presented to the ENT department with a 4 month history of nasal congestion, change in voice, snoring and right aural congestion.

Trans-oral examination and nasoendoscopy revealed a smooth mass arising from the right side of the posterior nasopharyngeal wall.

A CT scan was performed as a first line investigation which showed an ill- defined mass with a central hypodense area arising from the right tonsillar bed. The initial radiological impression was of tonsillitis.

MR neck was performed to further characterise the lesion – this showed a 39 x 51 x 33 mm pedunculated mass arising from the right nasopharynx – the differential being chordoma or fibroma.

Incisional biopsy was performed, no collection could be identified. A biopsy was sent for histological examination – this showed features of pleomorphic adenoma.

The lesion was removed surgically via the trans-oral route by dissection of the tumour from

the posterior aspect of the soft palate and nasopharyngeal mucosa. Histology of the lesion confirmed the finding of a pleomorphic adenoma.

The patient made an uneventful recovery with minimal post-operative morbidity.

Figure 1: *MRI images of the pleomorphic adenoma in the nasopharynx.*

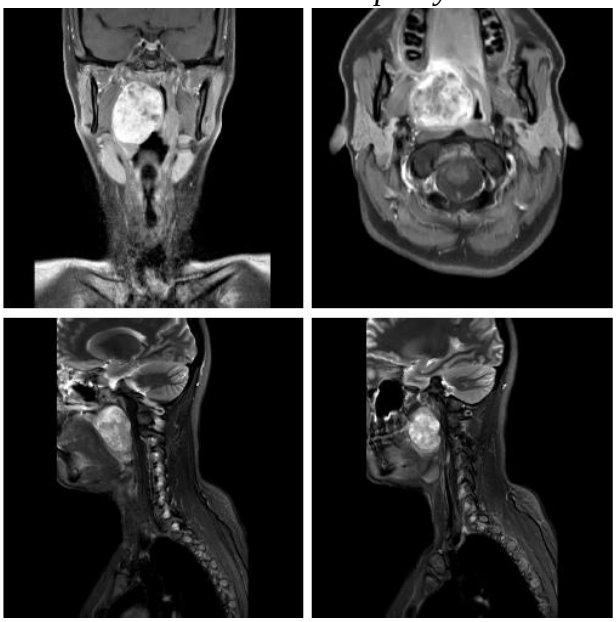
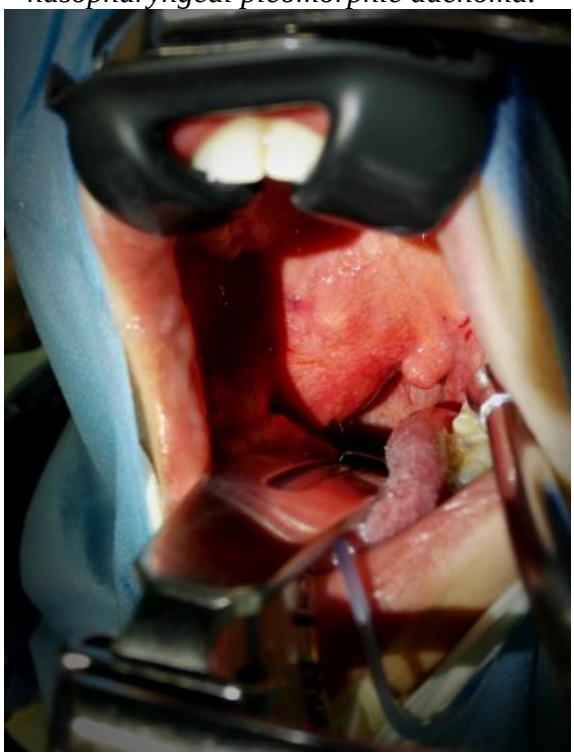


Figure 2:*. Bulging of uvula due to nasopharyngeal pleomorphic adenoma.*



Literature Review and Discussion

A PubMed search including the keywords: nasopharynx; nasopharyngeal; pleomorphic; adenoma resulted in 77 publications found. Upon review of these articles, 12 articles were identified of nasopharyngeal pleomorphic adenoma – from March 1970 to August 2015, two of which were congenital.

Management of the condition is varied. A number of reports have mentioned the transnasal endoscopic route for resection.[1-2] Others described a combined endonasal and transoral route.[3-4]

All reports treated the condition surgically. The only case which attempted to treat the condition with radiotherapy was unsuccessful.[5]

A completely transoral route for excision was not found anywhere. In this case, retraction of the uvula allowed for the tumour to be well visualised and it was removed with the surrounding capsule intact.

As in pleomorphic adenomas found in the parotid gland, it is essential to remove the tumour as a whole to avoid its recurrence.

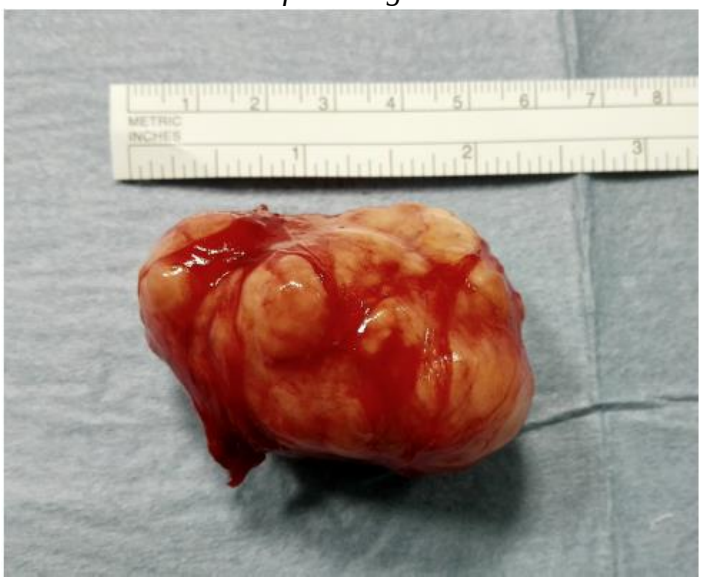
Conclusion

Nasopharyngeal pleomorphic adenoma is a rarely reported entity, and this is the first reported nasopharyngeal adenoma in a Maltese subject. A case of a pleomorphic adenoma of the nasal septum was described prior to this case in Malta. [6]

Diagnosis was made by clinical, radiological and histological means and removal of the tumour was performed via the transoral route, leaving an intact capsule.

The plan for the patient is to have regular post-operative surveillance visits with examination via flexible nasoendoscopy.

Figure 3: *Encapsulated Pleomorphic adenoma following removal*



References

1. Martínez-Capoccioni, G; Martín-Martín, C; Espinosa-Restrepo, F. Transnasal endoscopic resection of a nasopharyngeal pleomorphic adenoma: a rare case report. Eur Arch Otorhinolaryngol. 2012; 269(8):2009-13.
2. Berrettini, S; Fortunato, S; De Vito, A; Bruschini, L. A rare case of nasopharyngeal pleomorphic adenoma. Case Rep Otolaryngol. 2013; Article ID 712873.
3. Maruyama, A; Tsunoda, A; Takahashi, M; Kishimoto, S; Suzuki, M. Nasopharyngeal pleomorphic adenoma presenting as otitis media with effusion: case report and literature review. Am J Otolaryngol. 2014; 35(1):73-6.
4. Roh, J; Jung, B; Rha, K; Park, C. Endoscopic resection of pleomorphic adenoma arising in the nasopharynx. Acta Otolaryngol. 2005; 125(8):910-12.
5. Thakur, J; Mohindroo, N; Mohindroo, S; Sharma, D; Thakur, A. Pleomorphic adenoma of minor salivary gland with therapeutic misadventure: a rare case report. 2010; BMC Ear Nose Throat Disord. 10: 2.
6. Said, M; Griscti-Soler A; Deguara, J. Pleomorphic adenoma of the nasal septum: a case report. MMJ. 1996; 8(1) 39-40.