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Techniques and timings for cleft palate surgery: a randomised trial

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Abstract

Background: There is a lack of reliable information on outcomes following cleft surgery. Options for timing and choice of primary cleft surgery have not been compared in randomised trials.

Methods: Non-syndromic infants, aged six months, with isolated cleft of the secondary palate without associated lip deformity, were included in this prospective randomised controlled trial to one of four options: Veau-Wardill-Kilner palatoplasty at six months of age (VWK06) or 12 months of age (VWK12), or two-flap palatoplasty with intra-velar veloplasty at six months of age (2F-IVV06) or 12 months of age (2F-IVV12). Outcome measures are early and late postoperative complications, velopharyngeal inadequacy symptoms, nasality, articulation and presence of otitis media at three years of age.

Results: Of the 76 infants included in the trial, 90.8 per cent received surgery: VWK06 (n=18), VWK12 (n=16), 2F-IVV06 (n=18) and 2F-IVV12 (n=17). Early postoperative complications occurred in two VWK infants (6.1%) and three 2F-IVV infants (8.8%)—a difference of -2.8 per cent. With surgery planned at six months of age (T06) and 12 months of age (T12) respectively, there were three VWK infants (8.6%) and two 2F-IVV infants (6.3%)—a difference of +2.3 per cent. At age three, speech assessments were conducted for 62 (84%) children. Velopharyngeal inadequacy symptoms were detected in 4/30 VWK children (13.3%) and 3/30 2F-IVV children (10.0%)—a difference of 3.3. With T06 and T12, there were three VWK infants (9.4%) and four 2F-IVV infants (14.3%)—a difference -4.9%. Otitis media was documented in 40/61 of children (65.6%), hyper- and/or hyponasality in 27/61 of children (44%) and articulation errors in 53/60 of children (88%).

Conclusion: Post-surgical complication rates appear low, and differ little, between VWK and 2F-IVV. At three years, there were no demonstrable differences in velopharyngeal inadequacy symptoms, nasality, articulation and otitis media between the two surgical techniques at two different times.

Keywords: cleft palate, randomised trial, surgical timing, surgical technique

Introduction

Rates of cleft of the lip and/or palate vary within and between ethnic groups and, for the Chinese, rates range from 1.45 to 4.04 per 1000.[1] These defects may create problems in feeding, speech, hearing, dental development and facial growth. Despite surgical and multidisciplinary advances in cleft care, associated speech difficulties and facial appearance represent serious barriers to social integration.

At the time of preparing the protocol, there was a lack of information on outcomes following cleft surgery and options for primary cleft surgery were not compared in randomised trials.[2] Few centres used consistent approaches in technique, timing, sequence and ancillary interventions, making it impossible to identify the strategy providing the best results.[3]

In addition to the different timings of surgical repair and diverse surgical procedures, different outcome measures have been used to document success. Two of the outcomes of concern are dentofacial growth and intelligible speech with velopharyngeal adequacy. Consequently, a number of outcome scales and standards for reporting the results of surgery on individuals with clefts have been developed.[4-6]

While there remain many controversies in cleft surgery that could be resolved in randomised trials, key issues of technique and timing of palatal repair need to be resolved.[7] One non-randomised study of 51 children provided little evidence for the value of palatoplasty with intra-velar veloplasty (IVV) over palatoplasty alone.[8] In essence, much of the literature was of case series and was regarded as insufficient for sound, evidence-based medical practice.[9]

When reviewing the issues and controversies in the management of cleft palate, particular regard was paid to the timing of surgical intervention and the potential impact of palate repair on speech development. Controversy between early and late repair suggested that palatal surgery by 12 months of age may be associated with a lower incidence of speech problems.[10] Initiation of speech development begins at about six months age.[11] Should surgery therefore be performed at this early stage to maximise the developmental stage of speech development, or is surgery at 12 months of age sufficient to achieve adequate results? The surgical technique used plays a part in speech development and facial growth, with each technique offering different degrees of success.[12] Veau-Wardill-Kilner (VWK) palatoplasty aims to achieve adequate palatal lengthening to facilitate velopharyngeal competence. On the other hand, the two-flap palatoplasty in conjunction with a formal IVV (2F-IVV) is designed to reconstitute the palatal muscular sling which is claimed as essential for velopharyngeal adequacy speech. Early palatoplasty was purported to bring decreased otological episodes and more normal speech acquisition.[11,13]

A high incidence of otitis media with effusion is common in infants with cleft palate. Specifically, 92 per cent of 150 children aged 2 months to 18 months had otitis media before cleft palate repair, with this persisting in 70 per cent post-repair until the age of 4.[14]

The purpose of this prospective, multicenter, randomised controlled trial is to take note of early and late surgical complications and compare velopharyngeal inadequacy symptoms at three years of age following use of VWK or 2F-IVV for palate repair, at timings six months and 12 months.

Method

Trial design

A two by two factorial randomised controlled trial was used to compare postoperative complication rates and speech outcomes between VWK and 2F-IVV surgery given either at six months (T06) or

12 months (T12) age in the management of cleft palate without cleft lip.

Participants

Infants were eligible if they were aged less than six months and had isolated cleft palate. Written informed consent was obtained from the infant's parent/guardian before randomisation in accordance with national guidelines. The protocol was approved by the ethics committees of the participating institutions and conducted according to the Declaration of Helsinki. Infants were recruited from KK Women's and Children's Hospital, Singapore, and Chang Gung Memorial Hospital, Taipei, Taiwan.

Interventions

VWK palatoplasty

Incisions are made along the cleft margin and continued laterally along the posterior edge of the alveolus. The palatal mucoperiosteal flaps are then raised based on the greater palatine pedicle. The abnormal muscle insertions are identified and dissected off the posterior edge of the hard palate and the nasal layer superiorly to the junction of the middle and posterior third. The hamulus is then greenstick fractured to allow medial transposition of the mobilised musculature. The nasal layer is dissected off the edge of the hard palate and mobilised off the vomer before closure. The nasal layer is closed first, then the palatal myo-mucoperiosteal flaps are closed in a single layer with pushback. The releasing incisions made on the hard palate are left open and packed with SURGICEL® Original Absorbable Hemostat (Ethicon US, LLC, Bridgewater, New Jersey and Cincinnati, Ohio, USA).

2F-IVV

Incisions are made along the cleft margin and continued laterally along the posterior edge of the alveolus. The palatal mucoperiosteal flaps are then raised based on the greater palatine pedicle. The pedicle is next skeletonised after making periosteal incisions on either side of the pedicle. The mucoperiosteal flap is therefore islanded on the greater palatine vessels. The abnormal muscle insertions are dissected off the posterior edge of the hard palate and the nasal layer posteriorly to the junction of the middle and posterior third. The tensor is dissected off the hamulus with sharp dissection. The nasal layer is dissected off the edge of the hard palate and vomer and mobilised before closure. The nasal layer is closed first, then the muscle bundles are overlapped transversely and independently closed in a single layer. The palatal flaps are then returned to their original point anteriorly and closed with no pushback. The releasing incisions made on the hard palate are closed without tension.

Outcomes

Early (within 30 days) and late (within six months) postoperative complication data were captured. Speech assessments were scheduled to assess articulation and resonance at three years of age. Consonant production was evaluated in English using the Great Ormond Street Speech Assessment[15] to elicit sentence repetition and in Mandarin using standard pictures developed by Chang Gung Memorial Hospital. Participants were also asked to count from one to 20 and answer open questions (for example, 'Tell me who lives at home with you'). Speech data were recorded as an audiovisual and velopharyngeal inadequacy symptoms were categorised (see **Table 4**).[8] Nasality, overall intelligibility and articulation were also assessed.

The surgeons and speech therapists evaluating the outcomes were not blinded to the randomisation.

Trial size

Following VWK it was anticipated that the proportion of children with velopharyngeal inadequacy symptoms would be approximately 25–30 per cent at three years of age. Lowering this by 15 per cent with 2F-IVV would be of clinical importance. To detect such a difference, with a two-sided test of 5 per cent and power 80 per cent requires 120 infants assigned to each surgical procedure.[16] The factorial design implies that this number will also detect a similar difference in proportions with velopharyngeal inadequacy symptoms between T06 and T12.

Table 1: Trial profile by type and timing of surgery

	76 infants			
	VWK06	VWK12	2F-IVV06	2F-IVV12
Randomised: surgery and timing	17	18	17	19
Randomised: surgery only	–	1	–	1
Randomised: timing only	1	1	1	–
Allocated intervention	18	20	18	20
Parental consent withdrawn	–	2	–	1
Withdrawn by investigator	–	1	–	1
Not documented	–	1	–	1
Received surgery	18	16	18	17
Parental consent withdrawn	–	1	1	–
Audiological and surgical assessment (scheduled for age 18 months)	18	15	17	17
Parental consent withdrawn	–	–	–	2
Lost to follow-up	1	–	–	–
Surgical assessment (scheduled for age 36 months)	17	15	17	15
Parental consent withdrawn	1	–	–	–
Lost to follow-up	1	–	1	–
Audiological assessment (scheduled for age 36 months)	15	15	16	15
Lost to follow-up	–	1	–	–
Speech assessment (scheduled for age 36 months)	16	14	17	15

Veau-Wardill-Kilner type palatoplasty at six or 12 months (VWK06, VWK12), 2-flap palatoplasty with intra-velar veloplasty at six or 12 months (2F-IVV06, 2F-IVV12)

A complication rate at six months age of 10–15 per cent with each technique was anticipated and 120 infants would give a 95 per cent confidence interval (CI) for a zero difference between them of –9 per cent to +9 per cent.

Randomisation

Infants were allocated at random:

1. in a 1:1:1:1 ratio to VWK06, VWK12, 2F-IVV06 or 2F-IVV12
2. VWK or 2F-IVV if the timing of the surgery was selected by parent/clinical preference, or
3. T06 or T12 if the type of surgery was selected.

Randomisation was conducted by contacting the statistical office by telephone or using a web-based system.

Statistical methods

Velopharyngeal inadequacy symptoms and surgical complication rates were compared using the difference in the proportions between VWK and 2F-IVV, and T06 and T12, with 95 per cent CIs.

Results

Recruitment

Infants were enrolled from Singapore and Taiwan between 12 March 2002 and 18 January 2008. However, due to very slow recruitment, funding and logistical difficulties, the trial closed to recruitment without reference to the actual results but follow-up was continued until three years of age.

A total of 76 infants were recruited and allocated to VWK06 (n=12); VWK12 (n=20); 2F-IVV06 (n=18) and 2F-IVV12 (n=20) (Table 1). The majority, 71/76 (93.4%), were randomised between the four options. Surgery was chosen for three infants with timing randomised (VWK06, VWK12, 2F-IVV06), while two were randomised to surgery with fixed timing (VWK12, 2F-IVV12). Seven infants (6.8%), all T12, did not receive palatal surgery: three parents (3.9%) withdrew consent (two for VWK12, one for 2F-IVV12), two infants (2.7%) were withdrawn

Table 2: Demographics and characteristics of infants when allocated to options for surgery by timing

		VWK06	VWK12	2F-IVV06	2F-IVV12	All
Number of infants (n)		18	20	18	20	76
Centre	Singapore	11	14	11	12	48 (63.2%)
	Taiwan	7	6	7	8	28 (36.8%)
Age (months)	Mean	4.3	4.4	4.7	4.3	4.4
	Range	2.3–6.0	3.1–7.0	3.0–6.1	1.3–5.7	1.3–7.0
Gender	Male	5	6	8	7	26 (34.2%)
	Female	13	14	10	13	50 (65.8%)
Ethnicity	Chinese	14	18	15	18	65 (85.5%)
	Malay	2	2	3	1	8 (10.5%)
	Indian	2	–	–	1	3 (7.9%)
Cleft	Soft	7	7	7	7	28 (36.8%)
	Soft and hard	6	6	5	7	24 (3.6%)
	Soft, hard and incisive foramen	5	7	6	6	24 (31.6%)
Method of feeding	Spoon	2	3	4	2	11 (14.5%)
	Bottle	16	17	14	18	65 (85.5%)

Veau-Wardill-Kilner type palatoplasty at six or 12 months (VWK06, VWK12), 2-flap palatoplasty with intra-velar veloplasty at six or 12 months (2F-IVV06, 2F-IVV12)

by the investigator as one infant (VWK06) was constantly sick and the other had nasogastric tube-feeding because of dysphagia (2F-IVV12) and one VWK12 infant (1.3%) had an undocumented reason. Following surgery, two parents (2.7%) withdrew consent for one infant (2F-IVV06) at 27 days and a second infant (VWK12) at 7.2 months. At 36 months, three infants (3.9%) were lost to follow-up for audiology and a further one (1.3%) for the speech assessment.

Baseline data

The mean age at randomisation was 4.4 months (range 1.3–7.0), 50 infants (65.8%) were female and the majority were Chinese (85.5%) (**Table 2**). Location of the cleft palate was confined to the soft palate in 28 participants (36.8%), the soft and hard palate in 24 participants (31.6%) and the soft and hard palate with incisive foramen involvement in the other 24 participants (31.6%). Most infants (85.5%) were bottle-fed.

Surgical outcomes

The mean ages at palatal surgery for those destined for T06 and T12 were 6.3 months (range 5.4–7.6) and 11.4 months (range 10.2–12.9) and were also comparable between VWK and 2F-IVV (**Table 3**). Five of the 34 infants with VWK (14.7%) had deviation from their prescribed operation all with their lateral spaces closed. Of these, two VWK06 had no pushback and in one the flap repositioned naturally. Two of the 35 infants with IVV surgery (T06, T12) had no hard palate resection.

Prophylactic antibiotics were used in 20 infants (29.0%) and surgical blood loss was minimal (<50mL). The median duration of surgery was one hour (marginally longer at T06 than T12 with each surgical approach) and exceeded three hours in two: 2F-IVV06 (3.6 hours) and 2F-IVV12 (3.1 hours). The mean hospital stay was 2.8 days with only one exceeding 6 days (2F-IVV06).

Postoperative surgical complications

In all, 5/67 infants (7.5%) had postoperative complications within 30 days (**Table 3**):

- one infant (VWK06) had separation of the oral mucosa with palatal fistula formation
- one infant (2F-IVV06) had a small left oronasal fistula close to the uvula which was absent later
- one infant(2F-IVV06) had a partial dehiscence with a palatal fistula developing later, and

Table 3: Details of surgery by options for timing and postoperative complications within the first 6 months

		VWK06	VWK12	2F-IVV06	2F-IVV12	All
Operative details						
Number of infants	n	18	16	18	17	69
Age at surgery (months)	Mean	6.46	11.33	6.15	11.50	
	Range	5.36–7.62	10.35–12.39	5.45–7.16	10.15–12.91	
Deviation from described operation		2	3	1	1	7 (10.1%)
Prophylactic antibiotics given		6	3	7	4	20 (29.0%)
Duration of surgery (hours)	Median	1.13	0.89	1.15	1.12	1.00
	Range	0.50–2.92	0.60–1.50	0.58–3.63	0.63–3.17	0.50–3.63
Length of hospital stay (days)	Mean	3.00	2.69	2.78	2.88	2.84
	Range	2–4	2–4	2–6	2–5	2–6
Surgical complications						
Number of infants	n	18	15	17	17	67
Postoperative complications	Early: month 1	1	1	1	1	4
	Early and late	–	–	1	–	1
	Any	1	1	2	1	5 (7.5%)
Oronasal fistula present	By age 18m	1	–	1	–	2
	New by age 36m	–	–	1	–	1
	Any	1	0	2	0	3 (4.5%)

Veau-Wardill-Kilner type palatoplasty at six or 12 months (VWK06, VWK12), 2-flap palatoplasty with intra-velar veloplasty at six or 12 months (2F-IVV06, 2F-IVV12)

- two infants (VWK12, 2F-IVV12) had early postoperative bleeding, with the latter receiving a 70 mL transfusion.

No airway complications, infections or flap loss were reported.

The complication rates for VWK and 2F-IVV infants were 2/33 (6.1%) and 3/34 (8.8%)—a difference of –2.8% (95%, CI 15.5% to 10.3%). For T06 and T12, the rates were 3/35 (8.6%) and 2/32 (6.3%)—a difference of +2.3% (–10.7% to 15.3%). Surgical follow-up (**Table 3**) identified oronasal fistulas in two infants at 18 months of age (VWK06, 2F-IVV06) and one infant at 36 months of age (2F-IVV06).

Sixty-two children attended speech evaluation which was completed for all except two (2F-IVV06, 2F-IVV12) (**Table 4**).

In 34/61 infants (55.7%), neither hypernasality nor hyponasality was detected. In two infants (3.3%) only hyponasality was evident, 22/61 (36.3%) had varying degrees of hypernasality and a further three (4.9%) also had hyponasality. Audible nasal emission was inconsistent in 14/61 infants (23.0%) and consistent in two (3.3%).

Intelligibility was normal for 20 infants (33.3%) with 10 (16.7%) having speech 'only just intelligible to strangers' while in two (3.3%), both 2F-IVV06, speech was 'impossible to understand'. However, problems more severe than 'Different: Not enough to cause problems' were more prevalent with T06 at 17/33 (51.5%) than T12 at 12/27 (44.4%)—difference 7.1% (–28.0% to 42.2%). The difference between VWK at 14/30 (46.7%) and 2F-IVV at 15/30 (50.0%) was very marginal: –3.3% (–38.5% to 31.9%).

With respect to articulation, 50 infants (83.3%) had developmental errors either alone (70.0%) or combined with compensatory and/or other errors (13.3%). Only small differences between the surgical types and timings were apparent.

In 37/60 infants (61.7%) resonance was normal with type I (26.7%), type II (5.0%) and type III (6.7%). Velopharyngeal inadequacy symptoms were present in 11.7 per cent of infants, although this differed between nations (Singapore 7.9%, Taiwan 18.8%). Velopharyngeal inadequacy symptoms

Table 4: Speech and resonance outcomes at three years of age

Allocated surgical group		VWK06	VWK12	2F-IVV06	2F-IVV12	All
Age at asessment (y)	n	16	14	17	15	62
	Mean	2.96	3.17	3.07	3.13	3.08
	Range	2.41–3.17	2.84–3.85	2.78–3.99	2.88–3.90	2.42–3.99
Nasality hypernasality	n	16	14	17	14	61
Absent	Absent	9	6	10	9	34 (55.7%)
	Present	–	1	–	1	2 (3.3%)
Mild and occasional	Absent	5	2	5	2	14 (23.0%)
	Present	1	1	–	–	2 (3.3%)
Mild and consistent	Absent	1	2	1	1	5 (8.3%)
	Present	–	–	1	–	1 (1.6%)
Moderate and consistent	Absent	–	2	–	1	3 (4.9%)
	Present	–	–	–	–	–
Audible nasal emission	n	16	14	17	14	61
	Absent	13	8	13	11	45 (75.0%)
	Inconsistent	3	6	4	1	14 (23.0%)
	Consistent	–	–	–	2	2 (3.3%)
Nasal grimace	Present	1	–	–	1	2 (3.3%)
Intelligibility	n	16	14	17	13	60
	Normal	7	5	4	4	20 (33.3%)
	Different: not enough to cause comment	2	2	3	4	11 (18.3%)
	Different: mostly understandable	4	5	6	2	17 (28.3%)
	Only just intelligible to strangers	3	2	2	3	10 (16.7%)
	Impossible to understand	–	–	2	–	2 (3.3%)
Articulation	n	16	14	16	14	60
	Normal	2	1	2	2	7 (11.7%)
	Normal and developmental errors	2	–	3	–	5 (8.3%)
	Developmental errors	9	9	9	10	37 (61.7%)
	Developmental and compensatory errors	1	2	1	1	5 (8.3%)
	Developmental and other errors	1	1	–	1	3 (5.0%)
	Compensatory or other errors	1	1	1	–	3 (5.0%)
Velopharyngeal	n	16	14	16	14	60
Sufficient	Within normal limits	9	8	10	10	37 (61.7%)
	Marginal (I)	6	3	4	3	16 (26.7%)
Insufficient	Inadequate (II)	–	2	–	1	3 (5.0%)
	Inadequate (III)	1	1	2	–	4 (6.7%)
	Insufficient (%)	1 (6.3%)	3 (21.4%)	2 (12.5%)	1 (7.1%)	7 (11.7%)

Veau-Wardill-Kilner type palatoplasty at six or 12 months (VWK06, VWK12), 2-flap palatoplasty with intra-velar veloplasty at six or 12 months (2F-IVV06, 2F-IVV12)

Table 5: Audiological findings and audio-surgical interventions at age 18 months and 36 months

		VWK06	VWK12	2F-IVV06	2F-IVV12	All
Age (m) at 18 months assessment	**n**	18	15	17	17	67
	Mean	18.5	17.3	17.4	17.3	17.7
	Range	16.0–24.9	11.5–20.4	7.8–30.7	14.6–19.4	7.8–30.7
Age (m) at 36 months assessment	**n**	15	15	16	15	61
	Mean	34.7	34.2	35.1	35.3	34.8
	Range	28.8–38.4	21.9–46.2	31.1–39.6	28.1–41.5	21.9–46.2
Otitis media	**Absent**	8	3	4	6	21 (34.4%)
	At 18 months only	4	5	2	2†	13 (21.0%)
	At 36 months only	–	2	5	2	9 (14.5%)
	At 18 months and 36 months	3	5	5	5	18 (29.0%)
Bilateral myringotomy	**Not conducted**	5	3	7	5	20 (32.8%)
	At 18 months only	7	9 (1)‡	6	9	32 (52.5%)
	At 36 months only	1	1	1	–	3 (4.9%)
	At 18 months and 36 months	2	1	2	1	6 (9.8%)
Bilateral grommet tube insertion	**Non fitted**	6	4	6	6	22 (36.1%)
	At 18 months only	6	9	7	8	30 (49.2%)
	At 36 months only	1	(1)§	1	0	3 (4.9%)
	At 18 months and 36 months	2	1	2	1	6 (9.8%)

†No assessment at 36m. ‡ Additional infant,one ear. § One ear only. Veau-Wardill-Kilner type palatoplasty at six or 12 months (VWK06, VWK12), 2-flap palatoplasty with intra-velar veloplasty at six or 12 months (2F-IVV06, 2F-IVV12)

for VWK of 4/30 infants (13.3%) were higher than for IVV at 3/30 infants (10.0%)—a difference of 3.3% (–14.0% to 20.6%). For T06 velopharyngeal inadequacy symptoms were 3/32 infants (9.4%) but higher for T12 at 4/28 infants (14.3%)—a difference of –4.9% (–22.5% to 12.7%).

Audiological findings

Otitis media was documented in 31/67 infants (46.3%) by 18 months and a further nine (with five unknown) by 36 months, while, by this stage, it remained present in 27/62 infants (43.5%) (**Table 5**). Thus otitis media was noted on at least one occasion in 40/61 infants (65.6%). Rates differed little between VWK (63.3%) and IVV (65.5%) (2.3%, CI –21.5% to 26.1%) and between T06 (61.3%) and T12 (67.7%) (6.4%, CI –17.3% to 30.2%). Myringotomy had been conducted once (both ears) in 35 infants (57.4%) and was repeated in six (9.8%). Grommet tubes were inserted once (both ears) in 32 infants (52.5%) and a second time in six infants (9.8%). At this stage, the mean age of the 61 infants assessed was 34.8 months. There were no substantial differences noted between the surgical or timing options.

Discussion

In part, this trial was motivated by a keynote address[17] at the 12th Congress of the International Confederation of Plastic, Reconstructive and Aesthetic Surgery of prospects for new treatment and research strategies for the improvement of care of cleft lip and palate patients for the coming new millennium, as well as correspondence[18] following an editorial in *Plastic and Reconstructive Surgery*.[19]

The protocol for this randomised trial envisaged a complex and long-term follow-up schedule post primary surgery of (as appropriate), speech, hearing, orthodontic examinations and procedures

in infants with clefts of the secondary palate until they were aged 17 years. In the event, and without releasing trial data to the investigators, logistical difficulties within the participating centres and funding of the statistical support facilities combined with slow recruitment resulted in the decision to close the trial to recruitment but to continue recording the clinical outcomes until each child was three years old.

In retrospect, it is clear that this was a very ambitious and challenging trial to conduct and therefore it is perhaps of no surprise that it closed before the targeted number of children had been recruited. Several factors might have been anticipated. These include a rather complex protocol with burdensome demands on the amount of data to be recorded over time and hence insufficient focus on the key data elements necessary for the primary trial endpoints to be determined.

From a clinical trials perspective, the multifaceted care required for the children concerned made it intrinsically difficult to keep track of the follow-up examination pathways without dedicated personnel (specifically funded to support the trial) for coordination within each centre. These people could ensure liaison between the many clinical and care teams, provide support for the children and families concerned, link with the central statistical office and (as necessary) consult with the other recruiting centres. In addition, in the event of the inevitable investigator and other personnel changes, such individuals would ensure that their replacements were adequately briefed on the trial requirements. What is more, they would help identify children potentially eligible for the trial and remind the lead surgical investigators to review them for possible entry.

In our context with a trial conducted in two distant nations, the surgical teams were suitably trained in respect of the surgical techniques concerned but other aspects were not so rigorously standardised. Thus, an important suggestion for future trials is that a feasibility study[20] be conducted before the 'full' randomised trial is implemented. This would provide useful information to indicate modifications to the intended protocol and associated procedures. Testing at this pilot stage might include, for example, procedures for the speech or auditory evaluations intended for three years of age on current patients at that age within the centres concerned.

Also of help, because of the long-term nature of the trial involving children from infancy to late adolescence, would be the establishment of a small independent team of international and expert advisers to council the trial steering committee on any evolving consequences such as changing requirements in standards and methods of assessing and reporting speech development in a bilingual context over time.

Clearly a major difficulty is to ensure that the trial is adequately funded and over a considerable period of time. A trial that is under-resourced and hence, for example, does not have access to sufficient personnel for liaison purposes, is unlikely to succeed.

Of the 76 infants recruited, 69 (90.8%) received their surgery as allocated while seven were withdrawn by parents or investigators. That all seven of these withdrawals were T12 suggests that the method of randomisation was not optimal. It would have been better performed in two stages. Stage 1 randomise to T06 or T12. Stage 2, if allocated to T06 (immediate surgery), randomise immediately to VKK or 2F-IVV; but if allocated to T12 (delayed surgery), delay randomisation to VKK or 2F-IVV until the infant is 12 months age. The median duration of surgery was one hour (range 0.5–6.1), which differed little between the four intervention groups, as did the mean length of hospital stay of 2.8 days (2–6).

Surgical complication rates were lower than the 10–15 per cent anticipated and differed little between IVV (5.9%) and VWK (8.6%)—a difference of –2.7% (95% CI, –15.4% to 10.0%) for T06 (8.3%) and 2.3% (–10.4% to 14.9%) for T12 (6.1%).

Velopharyngeal inadequacy symptoms were lower with 2F-IVV (10.0%) than VWK (13.3%) at three years of age, although the observed lowering of 3.3 % (–14.0–20.6%) was less than the design specification. Rates were lower with T06 (9.4%) than T12 (14.3%) with a difference of –4.9% (–22.5

– 2.7%). Rates were much lower than the planning assumption with VWK (25%–30%) and also lower than the 22 per cent reported in patients (at unspecified ages) requiring pharyngoplasty.[21]

Otitis media was documented in 40/61 of children (66%) demonstrating the need for active monitoring of the middle ear to fully enable hearing and give the best access to speech and language development. At three years of age, 50/60 children (83%) displayed developmental errors related to their speech intelligibility.

Over the period since this trial was initiated, new developments have been made that would impact on the conduct of future multicenter, multinational randomised trials. For example, a framework to standardise perceptual speech production behaviour regardless of the spoken language has been elaborated.[22]

Conclusion

Although not achieving the planned recruitment, this trial concerning 76 infants was larger than the majority of 62 randomised trials (12 comparing surgical techniques) published between 2004 and 2013.[23] Our failure to complete this trial successfully, and the small number and small size of randomised trials comparing surgical interventions conducted, underlines the paucity of the available evidence-based information in this area. Nevertheless, this randomised trial does provide unbiased evidence that relatively low rates of velopharyngeal inadequacy symptoms are likely to be encountered, surgical complications with either VWK or IVV appear to be low and both findings seem to apply irrespective of the timing of surgery at six months or 12 months of age.

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