Journal of Clinical Orthopaedics and Trauma

Surgical Treatment of Spinal Stenosis in Achondroplasia: Literature Review Comparing Results in Adults and Paediatrics

--Manuscript Draft--

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Abstract:	Aims To assess the quantity and quality of available literature on surgical treatment outcomes of spinal stenosis in adult and paediatric achondroplasia patients through a systematic review of literature and to investigate the suitability of conducting a meta-analysis on outcomes of surgical treatment. Methods Online databases were searched according to PRISMA guidelines. No restrictions regarding study design, sample size, previous treatment, or publication date were implemented. The following terms: “Spinal stenosis”, “Spinal Decompression”, “Spinal fusion”, each term separately combined with the term “Achondroplasia” were used. Quality of the included studies were assessed used the Modified Coleman method. Results Five adult and four paediatric single-sample non-comparative studies were identified for inclusion (176 adult and 102 paediatric patients). Meta-analyses assessed the proportion of patients achieving full resolution of symptoms to be 0.51 (95% CI 0.00 to 1.00); the proportion of patients achieving full or partial resolution of symptoms to be 0.90 (95% CI 0.84 to 0.97); the proportion of procedures requiring re-operation to be 0.42 (95% CI 0.34 to 0.50; and the proportion of procedures involving dural tears to be 0.20 (95% CI 0.02 to 0.39). Statistical heterogeneity was very high for full resolution of symptoms and requirement for dural repair; and very low for other outcomes. Conclusions The available literature on this population and condition is sparse, highly heterogenous, and is generally of low quality limiting the value of meta-analysis. Overall, outcomes of surgical decompression of symptomatic spinal stenosis in achondroplasia patients show consistent degree of resolution of symptoms. Duration of symptoms prior to surgical treatment appears to play an important role in the overall

	outcome of treatment. Therefore, a delay in diagnosis and treatment can potentially be detrimental in achieving a better outcome.
Suggested Reviewers:	Chris Lewis cmblewis@googlemail.com
	Simon Woods simon.woods@doctors.net.uk
	Raghavendra Marappa-Ganeshan Raghu.mg@gmail.com
Response to Reviewers:	Response to reviewers: Manuscript title: Surgical Treatment of Spinal Stenosis in Achondroplasia: Literature Review Comparing Results in Adults and Paediatrics Dear reviewers, Many thanks for your detailed and useful feedback which we have read and responded to inline. Please also find attached an edited document of the revised manuscript which details changes made in response to your suggestions. Reviewer #1 comments: 1. GENERAL COMMENTS “This manuscript aims to report a nicely conducted systematic review and meta-analysis on the surgical treatment of spinal stenosis in achondroplasia in adult and pediatric population. Authors' efforts are commendable.” 2. ABSTRACT No remarks. 3. TITLE No remarks. 4. INTRODUCTION No remarks. 5. METHODS and MATERIALS Reviewer comment: “Please mention if the protocol for this review was published or preregistered, and provide registration details. Also mention the name and version of the software used for meta-analysis. Please mention formal metaanalysis technique(s) rather than Z test.” Authors’ response: Thank you for your comment. 1- The protocol was not published or preregistered. 2- The Z test for overall effect quoted is part of the standard set of statistical tests done for meta-analysis, as recommended by the Cochrane Collaboration: ‘In the context of Cochrane Reviews there are two commonly used statistical tests. The first is a test of overall effect (a Z-test), and its null hypothesis is that there is no overall effect of the experimental intervention compared with the comparator on the outcome of interest. The second is the (Chi2) test for heterogeneity, and its null hypothesis is that there are no differences in the intervention effects across studies.’ https://training.cochrane.org/handbook/current/chapter-15 This test was exactly the test we conducted. In fact, all the tests we conducted and quoted are those considered standard reporting by the Cochrane Collaboration. We

therefore do not consider it appropriate to remove any references to the Z test. Please note that the chi squared test recommended by the Chochrane Collaboration is the same as the test we used and referred to in our methodology under a different name “Cochran’s Q test”.

3- The software used for the statistical analysis has now been mentioned in the revised manuscript.

Changes to manuscript:

Page 4, lines 9-10: “Statistical analysis was conducted using Stata statistical software Version I/C 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). All results were summarised in tabulated form and in forest plots.”

6. RESULTS

Reviewer comments:
1- “The results section(adults part) mentions "Three out of five studies reported a total of 24 patients out of 105 (22%) to have documented previous spine surgery prior to their intervention" The nature of previous surgery and subsequent surgery, and reasons for the same need to be elaborated upon in more detail in tabular form.”

2- “Subsequently, it says "Whilst most patients in the adult group underwent decompression of spinal stenosis without instrumentation, 5 (3%) patients required instrumented fusion in addition to decompression." Please mention the indications/need and type for spinal instrumentation used in tabular form.”

3- “ ‘intra-operative dura tear occurred in 36% of patients’. Please elaborate upon the possible reasons for high risk of dural tears.”

Authors response: Thank you for your comments.

1- We have identified a mistake in the total number of patients of 24, upon review, the actual number is 26 and this has been corrected in the manuscript.

2- Where provided in the original paper, the nature of previous surgery has been added to table (1).

3- The indication and type of instrumentation was not given in the original paper by Carlisle et al. This has been clarified in table (1).

4- We have now elaborated on the possible reasons for the higher risk of dural tear in the discussion section, under the dural tear subsection.

Changes to manuscript and table (1):

Page 12, Lines 14-18:
“The reason for this increased risk of dural tear in Achondroplasia might be secondary to intrinsic, non-modifiable risk factors. These include anatomic sequelae of the underlying dysplasia, such as severity or chronicity of congenital stenosis, increased lumbar lordosis, horizontal positioning of the sacrum, and increased thoracolumbar kyphosis, which may predispose this unique group of patients to this complication.”

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Thoracolumbar
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	TLS2A022 THOMEER (2002)3639 (16-68)12-300Lumbar-036 AIN (2007)4939 (18-62)-Lumbar9B049 CARLISLE (2011)4937.7 (27-47)144Thoracolumbar-5D44 VLEEGEERT-LANKAMP (2012)2051.2 (21-67)37.5Thoracic15C020 TOTAL17639.9--265171 A: All previous procedures were laminectomies B: All previous procedures were laminectomies C: The nature of previous procedure was not described by the authors of the original paper D: The authors of the original paper did not describe the indication or type instrumentation used. 7. DISCUSSION Reviewer comments: “The discussion section says " in adults, recurrence of stenosis seemed to be the most common reason for re-operation" Please elaborate upon the reasons for restenosis.” Authors response: Thank you for your comment. We have now elaborated on the possible reasons for restenosis in the discussion section. Changes to manuscript: Page 11, lines 13-16: “Recurrence of stenosis in the previously decompressed spine might be attributed to accelerated facet hypertrophy, bony overgrowth and scarring. The accelerated hypertrophy may represent instability in the previously decompressed achondroplastic spine or some exaggerated response to normal motion resulting from the genetic defect of this condition.” 8. CONCLUSION No remarks. 9. REFERENCES No remarks. 10. FIGURES No remarks 11. TABLES See prior remarks Reviewer #2 comments: “Very well written manuscript.Good systemic review and metaanalysis.” No remarks on any section made by reviewer #2.

	Authors’ response: Many thanks, no further action taken.

Department of Orthopaedics
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Leeds
LS1 3EX

21st October 2021

Dear Dr Vaishya

Following the peer review process and the recommendation from reviewers to revise part of our manuscript, we have implemented changes and elaborated on the points raised in the review. We would be grateful if you would consider the revised version of our manuscript (*Surgical Treatment of Spinal Stenosis in Achondroplasia: Literature Review Comparing Results in Adults and Paediatrics*) for publication in the *Journal of Clinical Orthopaedics and Trauma*.

We confirm that this work is original and has not been published in whole or in part elsewhere, nor is it currently under consideration for publication elsewhere.

We can confirm that all authors have seen and approved the revised content, and all authors agree to submission to the *Journal of Clinical Orthopaedics and Trauma*.

I confirm that each of the listed authors meet each of the authorship requirements as stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

Thank you for your consideration of this manuscript.

Sincerely,
Zaid Abu Al-Rub

Response to reviewers:

Manuscript title: *Surgical Treatment of Spinal Stenosis in Achondroplasia: Literature Review Comparing Results in Adults and Paediatrics*

Dear reviewers,

Many thanks for your detailed and useful feedback which we have read and responded to inline. Please also find attached an edited document of the revised manuscript which details changes made in response to your suggestions.

Reviewer #1 comments:

1. GENERAL COMMENTS

"This manuscript aims to report a nicely conducted systematic review and meta-analysis on the surgical treatment of spinal stenosis in achondroplasia in adult and pediatric population. Authors' efforts are commendable."

2. ABSTRACT

No remarks.

3. TITLE

No remarks.

4. INTRODUCTION

No remarks.

5. METHODS and MATERIALS

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THOMEER (2002)	36	39 (16-68)	12-300	Lumbar	-	0	36
AIN (2007)	49	39 (18-62)	-	Lumbar	9[B]	0	49
CARLISLE (2011)	49	37.7 (27-47)	144	Thoracolumbar	-	5[D]	44
VLEEGEERT-LANKAMP (2012)	20	51.2 (21-67)	37.5	Thoracic	15[C]	0	20
TOTAL	176	39.9	-	-	26	5	171

A: All previous procedures were laminectomies

B: All previous procedures were laminectomies

C: The nature of previous procedure was not described by the authors of the original paper

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7. DISCUSSION

Reviewer comments:

"The discussion section says " in adults, recurrence of stenosis seemed to be the most common reason for re-operation" Please elaborate upon the reasons for restenosis."

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"Recurrence of stenosis in the previously decompressed spine might be attributed to accelerated facet hypertrophy, bony overgrowth and scarring. The accelerated hypertrophy may represent instability in the previously decompressed achondroplastic spine or some exaggerated response to normal motion resulting from the genetic defect of this condition."

8. CONCLUSION

No remarks.

9. REFERENCES

No remarks.

10. FIGURES

No remarks

11. TABLES

See prior remarks

Reviewer #2 comments:

“Very well written manuscript.Good systemic review and metaanalysis.”

No remarks on any section made by reviewer #2.

Authors’ response: Many thanks, no further action taken.

Surgical Treatment of Spinal Stenosis in Achondroplasia: Literature Review Comparing Results in Adults and Paediatrics

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Conflict of Interests: The authors declare that there is no conflict of interest.

Acknowledgments: None

Figure 1. Flowchart illustrating the selection of articles included in the review

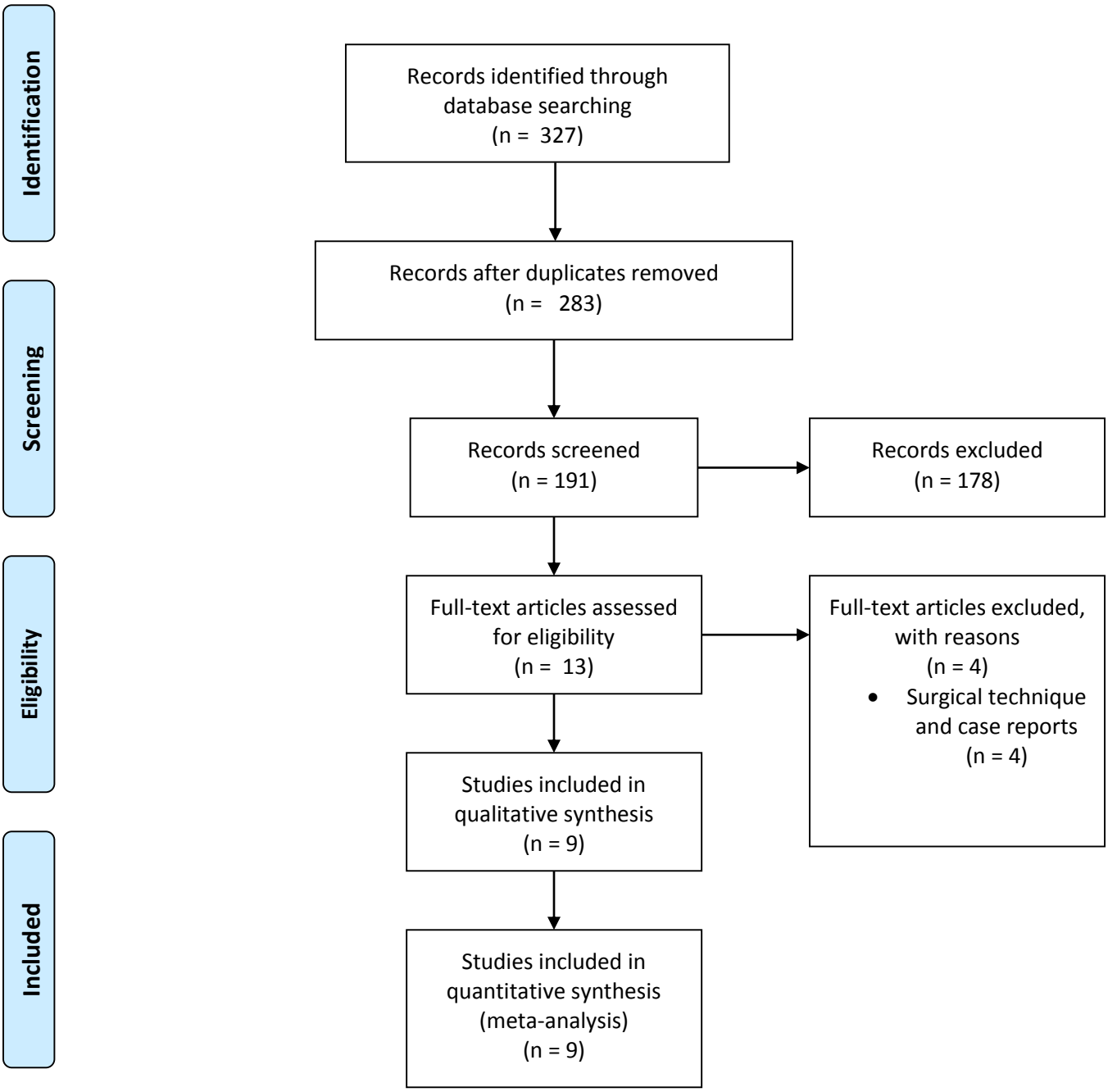


Figure 2. Forest plot for meta-analysis assessing proportion of adult patients experiencing full resolution of symptoms

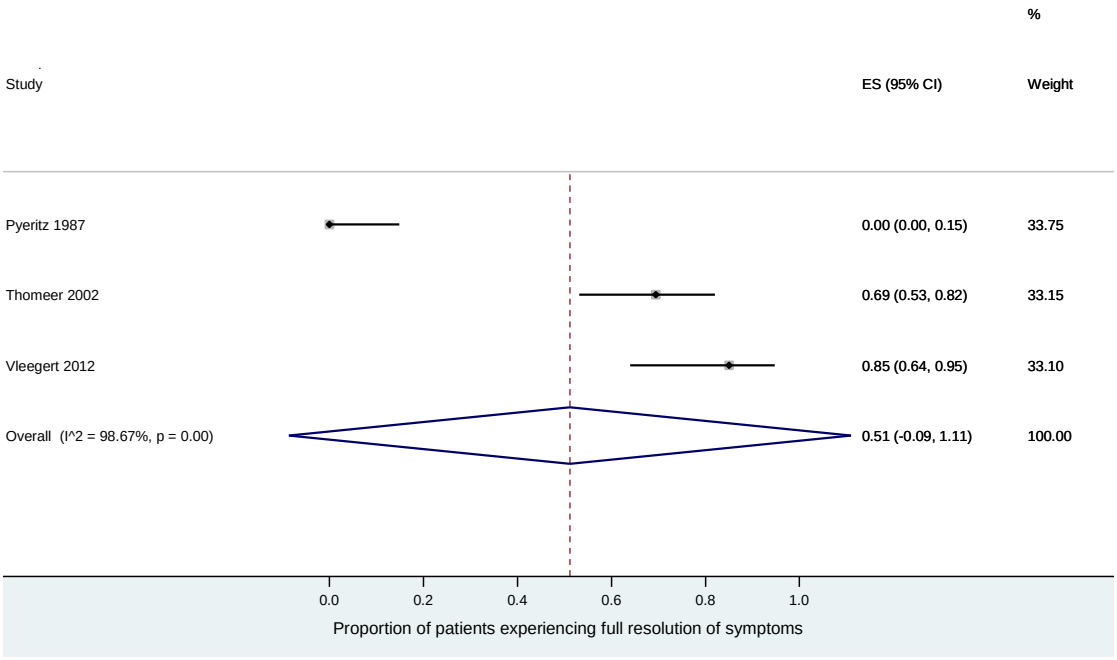


Figure 3. Forest plot for meta-analysis assessing proportion of adult patients experiencing full/partial resolution of symptoms

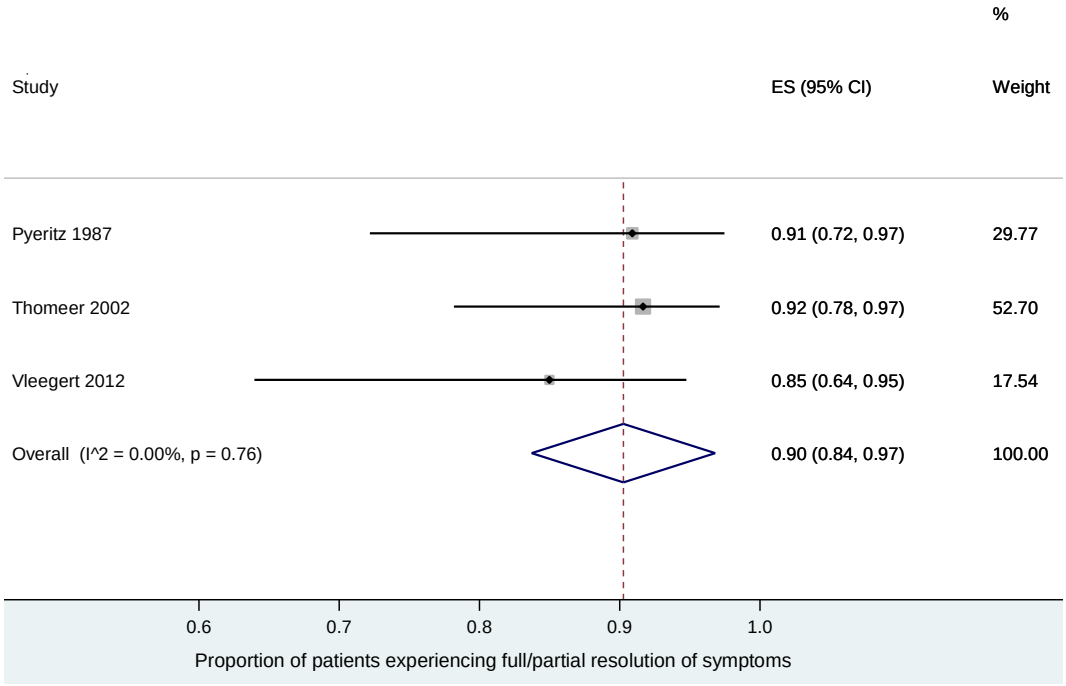


Figure 4. Forest plot for meta-analysis assessing proportion of procedures requiring re-operation in adults

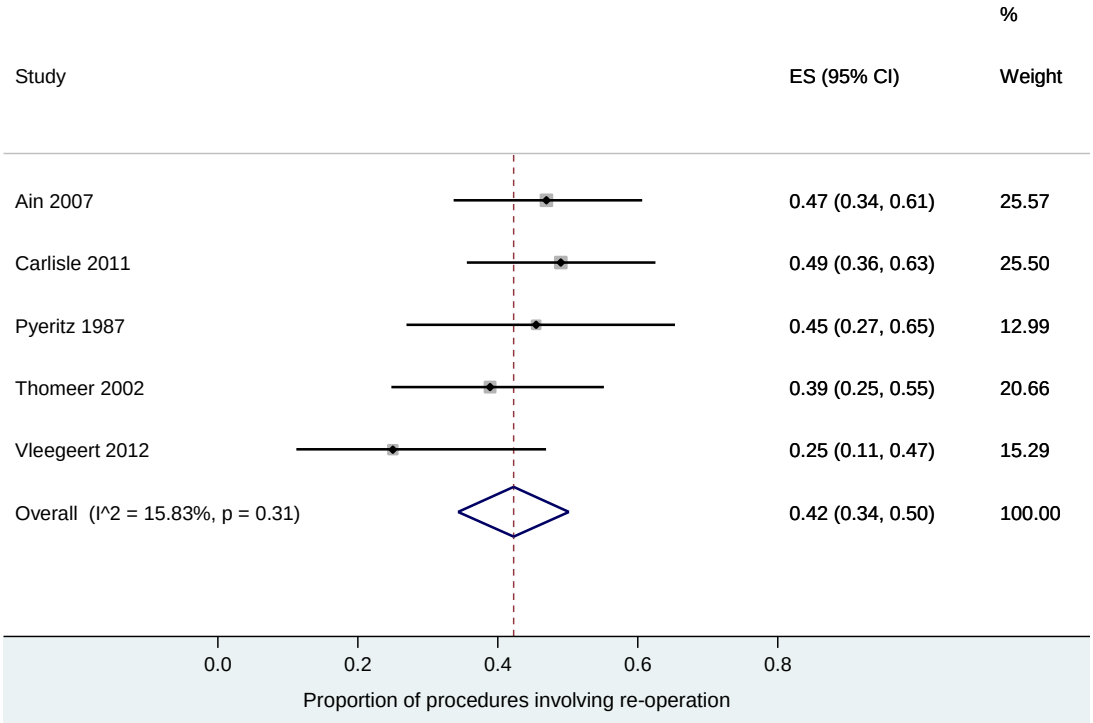


Figure 5. Forest plot for meta-analysis assessing proportion of procedures involving dura tear in adults

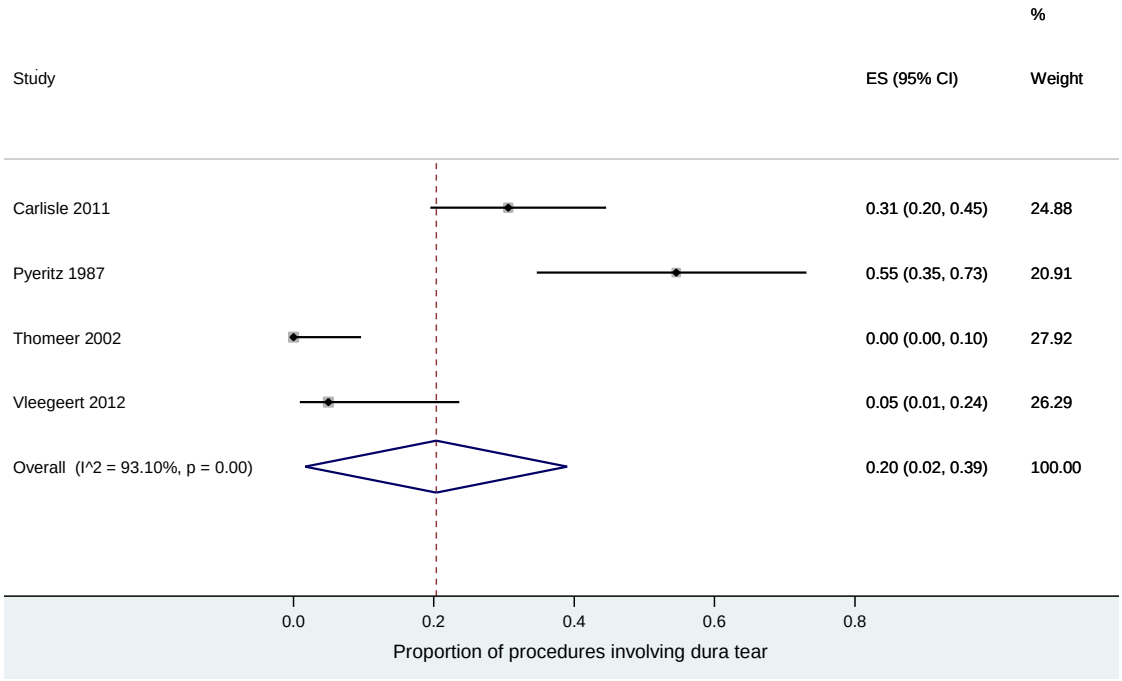


Figure 6. Forest plot for meta-analysis assessing proportion of paediatric patients experiencing full resolution of symptoms.

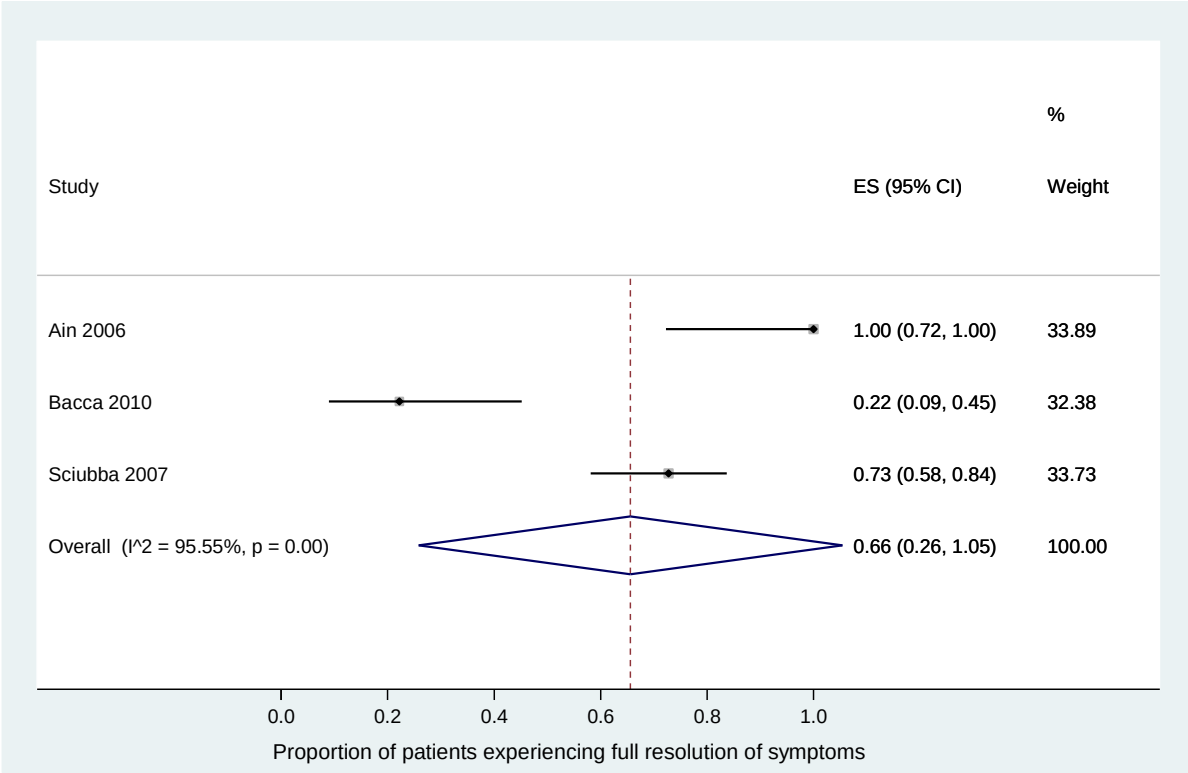


Figure 7. Forest plot for meta-analysis assessing proportion of paediatric patients experiencing full/partial resolution of symptoms.

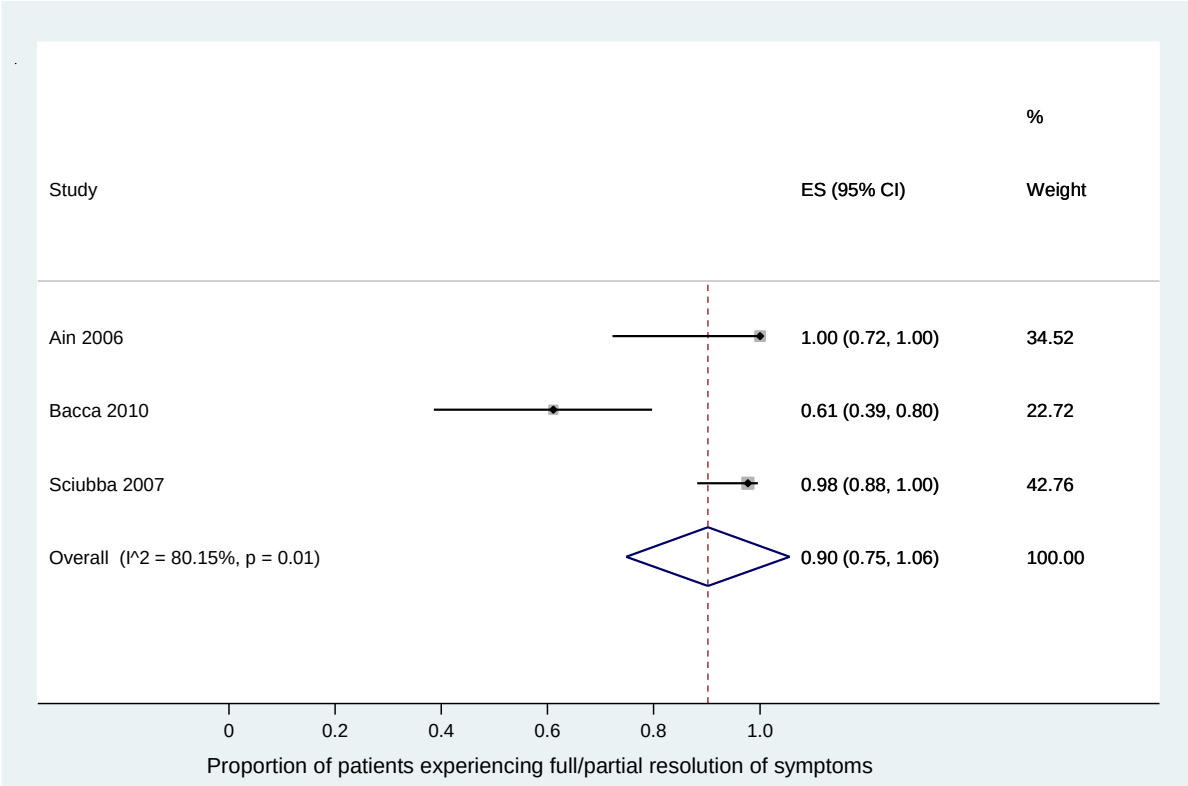


Figure 8. Forest plot for meta-analysis assessing proportion of procedures requiring re-operation in paediatrics

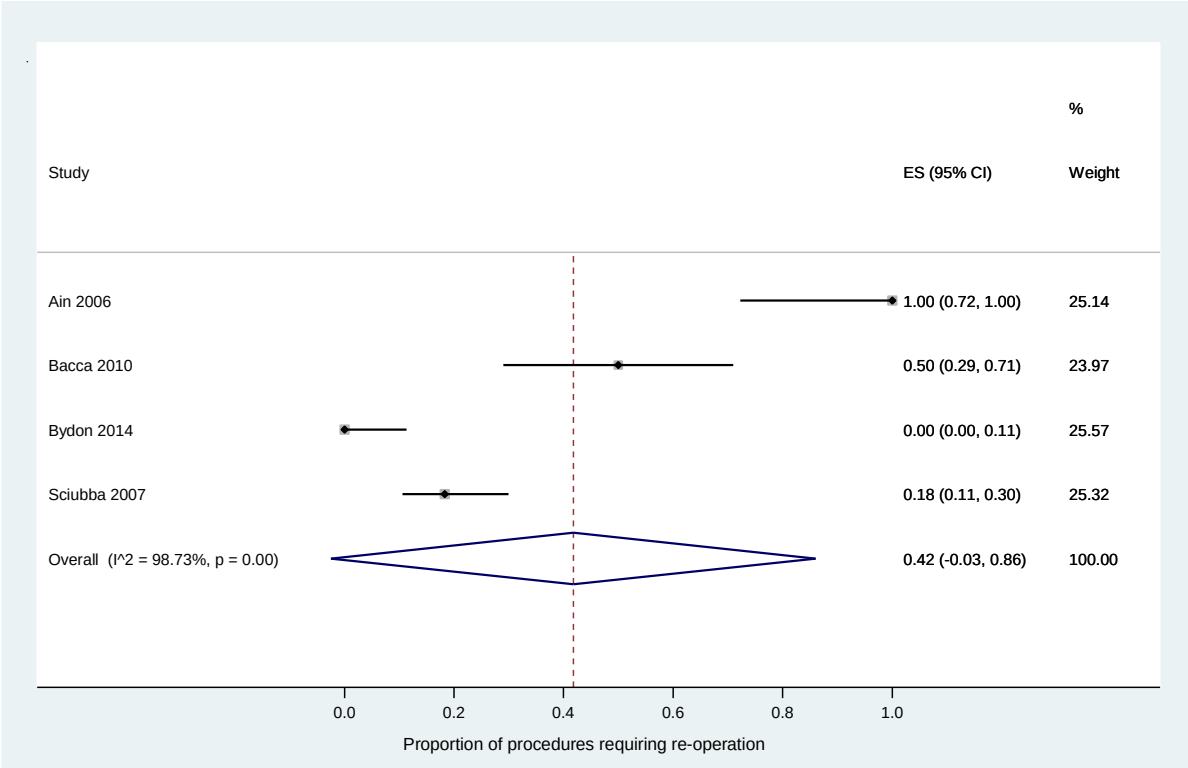
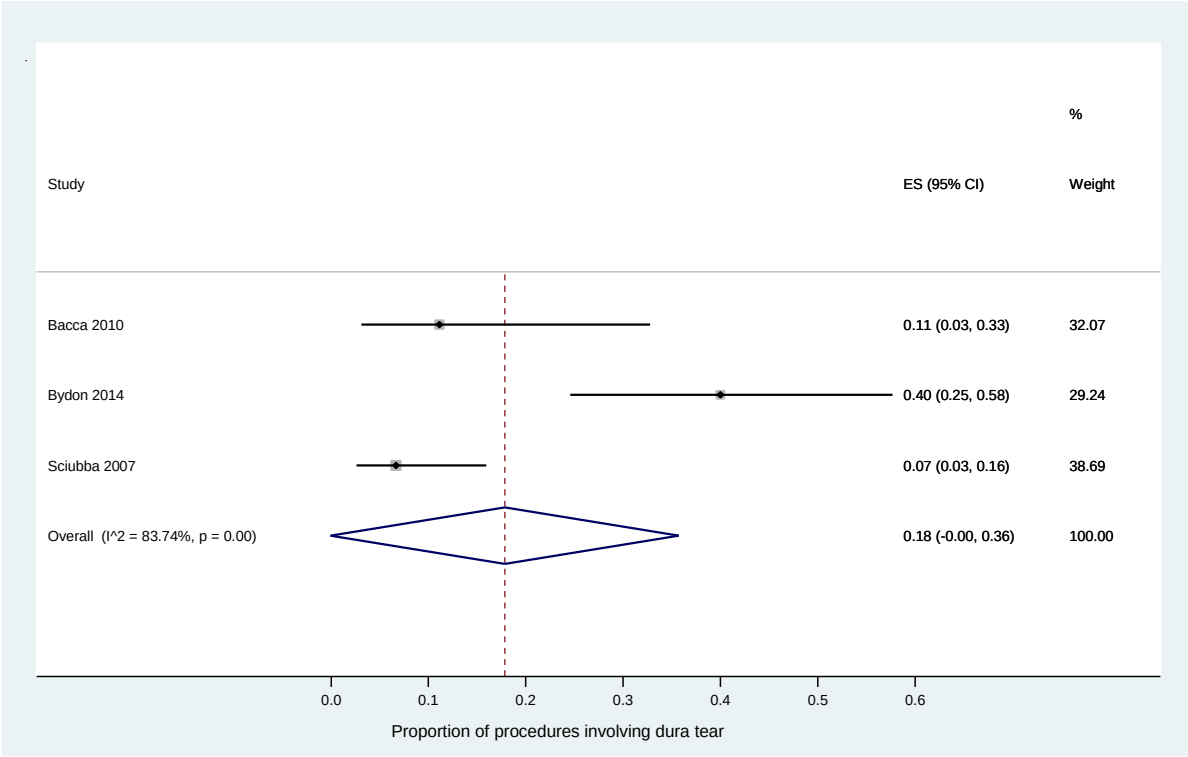


Figure 9. Forest plot for meta-analysis assessing proportion of procedures involving dura tear in paediatrics



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TOTAL	176	39.9	-	-	26	5	171

A: All previous procedures were laminectomies

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C: The nature of previous procedure was not described by the authors of the original paper

D: The authors of the original paper did not describe the indication or type instrumentation used.

Table 1. Adults - Outcomes and complications

STUDY	PROM	RESOLUTION OF SYMPTOMS (FULL/PARTIAL/NONE)	RE-OPERATION	DURA TEAR	POST-OP KYPHOSIS	DEEP INFECTION	WRONG LEVEL	NEUROLOGICAL SYMPTOMS PERSISTENCE OR DETERIORATION
PYERITZ (1987)	-	0/20/2	10	12	2	4	-	2
THOMEER (2002)	-	25/8/2	14	0	0	0	0	1
AIN (2007)	Rankin Walking distance	-	23	-	-	-	-	-
CARLISLE (2011)	Rankin	-	24	15	0	-	-	-
VLEEGEERT-LANKAMP (2012)	Nurick European Myelopathy Cooper mJOA Odom	17/0/3	5	1	-	0	3	3
TOTAL		42/28/7	78	28	2	4	3	6

Table 3. Summary of adult meta-analysis parameters

META ANALYSIS OUTCOME	SYNTHESISED ESTIMATE OF PROPORTION	95% CONFIDENCE INTERVAL	TEST FOR OVERALL EFFECT		HETEROGENEITY TESTING				
			z-statistic	p-value	Cochran's χ^2	df	p-value	I^2 statistic	τ^2 statistic
FULL RESOLUTION OF SYMPTOMS	0.51	(0.00, 1.00)	1.68	0.009	150.4	2	<0.001	98.7%	0.28
FULL/PARTIAL RESOLUTION OF SYMPTOMS	0.90	(0.84, 0.97)	27.0	<0.001	0.54	2	0.76	0.00%	0.00
RE-OPERATION	0.42	(0.34, 0.50)	10.5	<0.001	4.75	4	0.31	15.8%	0.00
DURA TEAR	0.20	(0.02, 0.39)	2.13	0.03	43.5	3	<0.001	93.1%	0.03

Table 4. Paediatric patients' characteristics and interventions

STUDY	SAMPLE SIZE	AGE	FOLLOW UP (MONTHS)	OPERATIVE LEVEL	PREVIOUS SURGERY	DECOMPRESSION + INSTRUMENTED FUSION	DECOMPRESSION ONLY
AIN (2006)	10	9.6 (6-16)	35 (10-48)	Lumbar	-	0	10
SCIUBBA (2007)	44 (60 procedures)	12.7 (5-21)	34 (8-93)	Cervical Thoracolumbar Lumbar	11	43	17
BACA (2010)	18	10.6 (7-18)	72 (44-100)	Lumbar	0	9	9
BYDON (2014)	30	14.5 (10-19)	21 (14-30)	Thoracolumbar	15	30	0
TOTAL	102 (118 procedures)	11.8	40.5	-	26	82	36

Table 5. Paediatrics - Outcomes and complications

STUDY	PROM	RESOLUTION OF SYMPTOMS (FULL/PARTIAL/NONE)	RE-OPERATION	DURA TEAR	POST-OP KYPHOSIS	DEEP INFECTION	WRONG LEVEL	NEUROLOGICAL SYMPTOMS PERSISTENCE OR DETERIORATION
AIN (2006)	-	10/0/0	10	-	10	-	-	-
SCIUBBA (2007)	-	32/11/1	11	4	5	2	0	4
BACA (2010)	-	4/7/7	9	2	9	-	-	3
BYDON (2014)	-	-	0	12	0	3	-	-
TOTAL		46/18/8	30	18	24	5	0	7

Table 6. Summary of paediatric meta-analysis parameters

META ANALYSIS OUTCOME	SYNTHESISED ESTIMATE OF PROPORTION	95% CONFIDENCE INTERVAL	TEST FOR OVERALL EFFECT		HETEROGENEITY TESTING				
			z-statistic	p-value	Cochran's χ^2	df	p-value	I^2 statistic	τ^2 statistic
FULL RESOLUTION OF SYMPTOMS	0.66	(0.26, 1.00)	3.23	<0.001	45.0	2	<0.001	95.6%	0.12
FULL/PARTIAL RESOLUTION OF SYMPTOMS	0.90	(0.75, 1.00)	11.5	<0.001	10.8	2	0.01	80.2%	0.01
RE-OPERATION	0.42	(0.00, 0.86)	1.85	0.06	235.8	3	<0.001	98.7%	0.20
DURA TEAR	0.18	(0.00, 0.36)	1.95	0.05	12.3	2	<0.001	83.7%	0.02
POST-OPERATIVE KYPHOSIS	0.39	(0.01, 0.77)	2.01	0.04	235.9	3	<0.001	98.7%	0.15
DEEP INFECTION	0.04	(0.00, 0.09)	2.04	0.04	n/a	n/a	n/a	n/a	n/a

Conflict-of-Interest Statement

Manuscript title: Surgical Treatment of Spinal Stenosis in Achondroplasia: Literature Review Comparing Results in Adults and Paediatrics

As the corresponding author, I declare on behalf of all co-authors that there are no conflict of interest related to this work.

Corresponding author (name/signature): Zaid Abu Al-Rub

Date: 08/02/2021

ABSTRACT

Background: This study aims to assess the quantity and quality of available literature on surgical treatment outcomes of spinal stenosis in adult and paediatric achondroplasia patients through a systematic review of literature and to investigate the suitability of conducting a meta-analysis on outcomes of surgical treatment.

Methods: Online databases were searched according to PRISMA guidelines. No restrictions regarding study design, sample size, previous treatment, or publication date were implemented. The following terms: "Spinal stenosis", "Spinal Decompression", "Spinal fusion", each term separately combined with the term "Achondroplasia" were used. Quality of the included studies were assessed used the Modified Coleman method.

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Conclusions: The available literature on this population and condition is sparse, highly heterogenous, and is generally of low quality limiting the value of meta-analysis. Overall, outcomes of surgical decompression of symptomatic spinal stenosis in achondroplasia patients show consistent degree of resolution of symptoms. Duration of symptoms prior to surgical treatment appears to play an important role in the overall outcome of treatment. Therefore, a delay in diagnosis and treatment can potentially be detrimental in achieving a better outcome.

Keywords: Achondroplasia; Stenosis; Spine; Adults; Paediatrics

INTRODUCTION

Achondroplasia, an autosomal-dominant condition with up to 80% of cases being a result of new sporadic gene mutation, is the most common form of skeletal dysplasia and the commonest type of dwarfism. This condition occurs due to a characteristic mutation in the gene encoding fibroblast growth factor receptor 3 (FGFR3) that results in inhibition of chondrocyte proliferation in the proliferative zone of the physis. [1,2]

Dwarfism, macrocephaly, frontal bossing, rhizomelic shortening of the extremities, and other skeletal abnormalities characterize achondroplasia.[3–6] Despite their musculoskeletal abnormalities, achondroplasia individuals have normal intellectual function. [2]

Neurological problems are frequent, and can be associated with significant functional limitations, and reduction in quality of life. This can be in many forms including delayed motor development, hydrocephalus, upper cervical cord compression, and spinal stenosis.

During *in utero* spine development, achondroplasia causes impaired longitudinal growth of the posterior arches due to a disorder in enchondral ossification which results in early fusion of the pedicles to vertebral bodies, accounting for shortened pedicles. The cross-sectional area of the spinal canal is consequently narrowed by the short pedicles and reduced interpedicular distance leaving reduced space available for the neural elements that eventually can lead to nerve root compression and spinal stenosis.[5,10–14]

Although narrowing in the lumbar spinal canal occurs in all achondroplastic spines, the incidence of developing neurological symptoms is variable and has been reported by different authors to range between 20-78% [2,15], with an estimated one third of the symptomatic population to require surgical intervention.

The purpose of this systematic review was to assess the quality and quantity of available published literature on spinal stenosis in adult and paediatric achondroplasia patients, and the explore suitability of conducting a meta-analysis on the outcomes of surgical treatment of spinal stenosis in this group of patients. Furthermore, we aim to compare the outcomes in terms of success of treatment, severity and frequency of complications encountered in adult and paediatric populations.

METHODS

A systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using the online databases Medline/Pubmed, The Cochrane Library, EMBASE, AMED, and CINAHL. Articles were identified using an electronic search of the following keyword terms: “Spinal stenosis”, “Spinal Decompression”, “Spinal fusion”, each term separately combined with the term “Achondroplasia”.

To be included, studies needed to be fully published in English language and reporting the results of one or more surgical treatment option for spinal stenosis in adult or paediatric Achondroplasia patients. There were no restrictions regarding study design, population size, previous treatment, intensity or duration of symptoms, or publication date.

We excluded case reports, morphometric, and technique comparative studies.

Data from each included study was extracted. The following information was recorded: age, follow-up duration, duration of symptoms, symptoms (motor and/or sensory deficits, neurogenic claudication, radicular pain, bowel and/or bladder dysfunction), previous surgery, type of procedure, patient reported outcomes, resolution of symptoms (full, partial, none), re-operation, type of consequent surgery if any, interval time to re-operation, complications (dura tear, kyphotic deformity, deep infection, wrong level decompression) and return to work if applicable.

To assess the quality of the studies included in our review, two independent authors (ZA, BL) used the Modified Coleman Methodology which results in a score between 0 and 100.[17,18] In our data analysis, when an outcome measure was not reported by the authors, their cohort was excluded from our statistical analysis for that specific outcome to avoid making any assumptions.

Meta-analyses methods

Single-proportion random effects meta-analyses were conducted on the following outcomes: full resolution of symptoms; full/partial resolution of symptoms; re-operation; dura tear. Meta-analyses were not conducted on other measured outcomes (post-operative kyphosis; deep infection, wrong level) due to these events being recorded at non-zero levels in only one study each. All meta-analyses conducted used the number of patients as the denominator.

In each meta-analysis, a synthesised estimate for the proportion of patients or procedures associated with the event of interest, with an associated 95% confidence interval (CI) was derived. A *Z*-test for overall effect was also conducted and reported. Heterogeneity was assessed using Cochran's Q test, the I^2 statistic and the τ^2 statistic (between-study variance). Statistical analysis was conducted using Stata statistical software Version I/C 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). All results were summarised in tabulated form and in forest plots.

RESULTS

In total, 327 articles were retrieved through the primary search. The articles were screened by title and abstract for relevance. A total of 42 articles were found to be of relevance to the subject of the study. The full text was retrieved for further analysis of the aforementioned studies. Following application of the exclusion and inclusion criteria, 9 articles suitable for the purposes of this systematic review remained. Five studies were focused on adults and the other four were concerned with paediatric population of patients. The vast difference between adults and paediatrics regarding the anatomy and physiology of their skeleton dictated us to interpret and report the results of each population separately.

Figure 1. Flowchart illustrating the selection of articles included in the review

The average Modified Coleman Methodology score for adult studies was 41.6 versus 37.7 out of 100 for paediatric studies.

The total number of patients in the adult cohorts was 176 patients with an average age of 39.9 years, and 102 patients from the paediatric cohorts with an average age of 11.8 years. In adults, patient follow-up ranged between the included studies from 1 to 25 years, while in the paediatric studies it ranged from 8 months to 8.3 years. Lumbar spine, followed by thoraco-lumbar were the most common operated segments of spine in both adult and paediatric cohorts.

Adults Results

The average duration of symptoms was reported in 4 out of 5 studies and was 4 years and 9 months prior to treatment. Patients were reported to have variable symptoms, with neurogenic claudication being the most common presenting symptom reported in 57% of adult patients. Sensory and motor deficit were reported in 30% and 15% of patients respectively, while bladder and/or bowel dysfunction was present in 32% of patients.

Three out of five studies reported a total of 26 patients out of 105 (25%) to have documented previous spine surgery prior to their intervention. [19, 21, 23]

Whilst most patients in the adult group underwent decompression of spinal stenosis without instrumentation, 5 (3%) patients required instrumented fusion in addition to decompression.

Table 1. Adult Patients' characteristics and intervention

Table 2. Adults - Outcomes and complications

When resolution of symptoms following surgical intervention was reported, full resolution was observed in 54% of patients, whilst 37% had partial resolution, and 9% showed no improvement in their pre-operative symptoms.

Pyreitz et al reported 2 out of 20 patients with no improvement in neurological symptoms. One patient developed paraplegia following second laminectomy which persisted despite third attempt to release compression. [19] Thomeer et al reported one case of deteriorating neurological status with diminished bladder

control which was secondary epidural haematoma. [20] Vleggeert-Lankamp et al reported 3 cases that failed to demonstrate neurological improvement to wrong-level operation. [21]

As demonstrated in table (2), Patient Reported Outcomes (PROMs) were reported in three studies.[20–22] Odom criteria analysis of the patient outcome scores showed that in a study of 20 patients, 25% showed no change or worsening in their symptoms postoperatively, while 75% had partial or full resolution of their symptoms. In the same study, functional status was observed to improve by 1 point on the Cooper scale in 8 out of 20 patients (40%), while 12 out of 20 patients (60%) maintained same level of function post-operatively. No cases showed deterioration in function.[21]

The overall walking distance improved post-operatively as demonstrated in a study of 49 patients. This seemed to be strongly correlated with the duration of symptoms pre-operatively. Patients with symptom duration of less than 6 months before their first laminectomy (14 out of 49 participants [28.6%]) had 7 times better chance to experience improvement in walking distance and were 4 times more likely to experience a decrease by at least one full Rankin level than those who had had symptoms for greater than 6 months, reflecting greater independence.[20]

The reported post-operative complications are demonstrated in Table (2). The rate of re-operation for any complication, recurrence of symptoms or failure to resolve symptoms was 44%, while intra-operative dura tear occurred in 36% of patients.
Post-operative kyphotic deformity was noted in 2 patients only, and deep infection in 4 patients, whilst 3 patients underwent surgical intervention at the wrong spine level.

Adult Meta-analysis results

The estimates extracted from each of the meta analyses conducted on the included adult studies is summarised in Table (3) and Figures (2-5) below.

Table (3). Adults - summary of meta-analysis parameters

Pyeritz et al. (1987) reported in their case series promising results in the first 6 months of follow-up, with high rate of return of bladder function and muscle strength provided decompression occurred within few weeks of symptoms onset or deterioration. However, the long-term results were mixed, and the authors noticed that narrow laminectomy was associated with a high rate of re-stenosis (41%) and post-operative hypertrophic scarring at one or more levels of the original laminectomy. The authors reported that 2 out of 22 (9%) patients in this cohort underwent fusion secondary to developing post-operative kyphotic deformity.[23]

A study of 36 cases who were treated with widening lumbar interapophyseolaminar diameter without laminectomy reported full resolution of symptoms in 71% of patients, while 23% remained with tolerable symptoms and 6% had no benefit from surgery. However, 14 out of 36 (39%) patients required further surgical interventions due to inadequate relief of symptoms. There was no mention by the authors of how many procedures performed in the group of patients who had full resolution of symptoms initially. [19]

Figure 2. Forest plot for meta-analysis assessing proportion of adult patients experiencing full resolution of symptoms

Figure 3. Forest plot for meta-analysis assessing proportion of adult patients experiencing full/partial resolution of symptoms

In a retrospective study of 8 patients who had clinically significant re-stenosis at previously decompressed levels, instability was identified in 4 patients (50%) due to previous facetectomy or extensive foraminotomy. Two patients had no pre-operative kyphosis and were treated with transverse process fusion and external orthosis, while the other two (25%) had kyphotic deformity and required fusion with instrumentation. [24]

Figure 4. Forest plot for meta-analysis assessing proportion of procedures requiring re-operation in adults

Figure 5. Forest plot for meta-analysis assessing proportion of procedures involving dura tear in adults

Paediatrics Results

In the paediatric cohorts, two-thirds of the patients were found to have motor weakness, neurogenic claudication and sensory deficit, while less than half were reported to have bladder or bowel dysfunction. The least common symptom was radicular pain, reported in nearly 1 out of 5 patients. As reported in three studies[25–27], 26 out of 92 patients (28%) had had previous spine surgery. Out of 118 procedures, 70% included instrumented fusion.

Table 4. Paediatric patients' characteristics and intervention

None of the studies included a patient-reported or functional outcome tool to report the outcome of their intervention.

Full resolution of symptoms was reported in 46/72 (67%) of patients, whilst 25% experienced partial resolution, and 8% had no improvement. Revision surgery was required in 20 out 72 (28%) of patients.

Bydon et al reported statistically significant resolution of neurogenic symptoms in all their patients compared to the baseline status following surgical intervention with neurogenic claudication, weakness, and radiculopathy showing complete resolution. [25,] Baca et al reported improvement in claudication, weakness, numbness, incontinence, and abnormal reflexes in 61%, 56%, 50%, 72% and 33% of their patients respectively. Three out of 18 patients (16%) developed new onset neurologic symptoms with 2 patients showing new-onset weakness and 1 patient with new-onset abnormal reflexes. [27] Sciubba et al reported persistence of myelopathic symptoms in 1 patient despite adequate decompression and no evidence of stenosis at different level on MRI and new-onset radiculopathy in 3 patients, two of which were treated conservatively and one patient underwent repositioning of pedicle screw with resolution of symptoms afterwards.[26]

In the combined results of all studies, the most common encountered complication recorded post-operatively was the development of spine kyphotic deformity. This was reported in 24 out of 102 patients (23.5%); followed by intra-operative dural tear, which occurred in 18 out of 92 (20%) patients. Deep infection was reported in 2 studies and affected 5 out 77 patients (6.5%), while no patients underwent surgical intervention at the wrong level.

Table 5. Paediatrics - Outcomes and complications

Paediatrics Meta-analysis Results

The estimates extracted from each of the meta analyses conducted on the included studies is summarised in Table 6 and figures 6-9 below.

Figure 6. Meta-analysis summary of proportion of paediatric patients experiencing full resolution of symptoms.

Figure 7. Meta-analysis summary of proportion of paediatric patients experiencing full or partial resolution of symptoms

In a retrospective study of 44 paediatric patients with an average age of 12.7 years who underwent a total of 60 surgical decompression procedures, 43 (72%) procedures involved instrumented fusion and autograft, revision surgery was required in 11 (25%) cases. [26]

In 2010, another study including 18 paediatric patients of which 9 patients were skeletally immature (Risser grade <5) and received instrumentation in addition to decompression, revision surgery was required by 9 (50%) of the cases. Seven out of nine (78%) revision cases were for patients who underwent decompression without instrumentation. All revisions were due to progressive and symptomatic kyphotic deformity with abnormal sagittal profile that required instrumentation.[27]

Figure 8. Forest plot for meta-analysis assessing proportion of procedures requiring re-operation in paediatrics

A meta-analysis of dural tear in paediatrics demonstrated in figure (9) was reported in 3 studies.[25–27] Between the studies, intra-operative dural tears ranged from 6-40%.

Figure 9. Forest plot for meta-analysis assessing proportion of procedures involving dura tear in paediatrics

DISCUSSION

This study analysed the available literature on achondroplasia patients who were treated surgically for spinal stenosis. To our knowledge, there has been no previous systematic reviews on this condition and group of patients published in literature.

Our review demonstrated that the quantity of literature available on this topic is limited and of overall low quality. In addition, the high heterogeneity and variability in reporting outcomes between the studies made the results of a meta-analysis not reliable to draw conclusions.

The results of our review showed that the outcomes of surgical decompression for spinal stenosis in adults and paediatrics with achondroplasia are favourable with regards to resolution of symptoms, improvement in function and greater independence and patients who presented within 6 months from the onset of their symptoms appeared to have better results. Nonetheless, surgical treatment of spinal stenosis in this unique group of patients can be associated with significant risks of intra- and post-operative complications that must be acknowledged in the process of counselling and consenting of patients offered surgery. Recurrence of stenosis, at the same site or junctional, was a common complication encountered that often lead to repeated surgical interventions and further decompressions which expectedly showed a higher risk of complication, as well as, a risk of spinal destabilisation when more levels were decompressed. In skeletally immature achondroplastic patients, there is significant potential advantage in favour of instrumented stabilisation over decompression alone in order to prevent the development of spinal deformity.

Resolution of symptoms

In the general population with degenerative spinal stenosis, good surgical results have been reported in 68% of patients after a mean follow-up period of 12 years.[28,29] Despite this, up to 20% of patients undergoing primary surgery for spinal stenosis do not experience sustained symptomatic pain relief.[30]

In our comparison of the adult achondroplasia results to the paediatric group with regards to resolution of symptoms, we found that spinal decompression had a similar success rate in resolving symptoms as revealed by the meta-analyses, and the synthesised estimates for the outcome measures were broadly comparable to

those generated from a parallel analysis of paediatric patients. The proportion of adult patients estimated to experience full or partial resolution of symptoms, at 0.90 was in fact identical to the corresponding figure derived in the parallel paediatric study, which also generated an estimate of 0.66 for the proportion of paediatric patients estimated to experience full resolution of symptoms.

Risk of re-operation

On the other hand, the estimates of re-operation and dura-tear occurrence in the study of adult patients (0.42 and 0.20) were also almost identical to the corresponding estimates in the study of paediatric patients (0.42 and 0.18).

In adults, the re-operation rate reported by different authors ranged from 25%-45%, which is slightly less than but comparable to what we found in the paediatric group of patients that ranged from 25-100% between studies. Whilst post-operative spinal deformity, mostly kyphotic, was the main reason for re-operation in children, in adults, recurrence of stenosis seemed to be the most common reason for re-operation. Recurrence of stenosis in the previously decompressed spine might be attributed to accelerated facet hypertrophy, bony overgrowth and scarring. The accelerated hypertrophy may represent instability in the previously decompressed achondroplastic spine or some exaggerated response to normal motion resulting from the genetic defect of this condition. [24] The variation in rate of re-operation in the paediatric group might be explained by the results of 10 skeletally immature achondroplasia patients with an average age of 9.2 years who underwent multilevel thoracolumbar laminectomies of 5-8 levels and demonstrated a 100% progressive postoperative thoracolumbar kyphosis (mean 94°, range 78°-135°). All patients underwent a second procedure and instrumentation was performed at an average of 13.2 months from the primary procedure.[31] Those results from a single study might skew and overestimate the actual rate of revision or re-operation in the paediatric group overall. Equally, the outcomes of this particular study is of significance as it demonstrated the potential significant importance of using instrumentation in the growing spine, an observation that is not felt to be similar significance in the adult group.

Progressive spinal deformity

Post-operative spine progressive deformity in children was a frequently observed outcome when primary spinal decompression was performed without instrumented stabilisation. In one study, this was reported in 100% of the patients.[31] However, a similar outcome was not observed in the adult population. In contrast to children, post-operative deformity was reported in one adult study, affecting 2 out of 22 (9%) patients only.[23] Several reasons can be attributed to this. The anatomical difference between children and adults, mainly represented by the ongoing axial and peripheral skeletal growth in children, providing a dynamic environment in contrast to the static environment found in a skeletally mature adult. Nonetheless, multiple other factors must also be taken into consideration, and that includes the number of levels decompressed in each case, as well as, the method of decompression. Also, the possibility of under reporting by authors in the adult studies, and the difference in follow-up time between studies, are all factors that could potentially mask the true incidence of post-operative deformity in adults.

Dural tear

Intra-operative dural tear incidence was highly variable in general. In the adult group, it ranged between 5-55% of cases, while in the paediatric group, it ranged from 6% to 40%. In comparison, the incidence of dural tear in general non-achondroplasia patients with spinal stenosis appear to be lower, with incidental durotomy rates in the published literature ranging from 3.5% for primary discectomy and 13.2% for revision discectomy in adult populations,[32] with 0.34% in index procedures and up to 18.5% in revision operations in paediatric populations.[33] The reason for this increased risk of dural tear in Achondroplasia might be secondary to intrinsic, non-modifiable risk factors. These include anatomic sequelae of the underlying dysplasia, such as severity or chronicity of congenital stenosis, increased lumbar lordosis, horizontal positioning of the sacrum, and increased thoracolumbar kyphosis, which may predispose this unique group of patients to this complication. [34]

Comparing ultrasonic bone curette (BoneScalpel) in 10 patients versus high-speed drill in 20 patients in a retrospective review of 30 paediatric achondroplastic patients who were treated for spinal stenosis using showed a decreased number of durotomies and overall complications in the ultrasonic bone curette

(BoneScalpel) cohort versus the high-speed drill cohort. Those results originate from a single study with small number of patients, therefore definitive conclusions cannot be made about the superiority and protective effect of the ultrasonic bone curette device over the high-speed drill.

Neurological recovery

The recovery of neurological symptoms such as neurogenic claudication, weakness, numbness, incontinence or abnormal reflexes was variably reported between studies.

Across all studies reporting on the neurological status post-operatively, the majority of patients showed improvement in their symptoms with variable degree of sustainability. In the early post-operative phase, in cases where no improvement is observed or new onset neurological deficit is noticed, further investigations are warranted to rule out the possibility of wrong level surgery or suboptimal positioning of pedicle screws when used. In the longer term, recurrence of stenosis or junctional stenosis should be considered and investigated, especially in when symptoms are not tolerated by patients.

The body mass index (BMI), duration of symptoms, time to surgery and degree of pre-operative kyphotic deformity were amongst other factors studied in the literature.

In a study of 49 patients, the body mass index (BMI) was found to have no significant effect on the functional and surgical outcomes including: walking distance, intra- or post-operative complications, and subsequent revision laminectomy.[22]

In thoracic spine, a kyphotic angle greater than 40° was suggested to be the threshold for spondylodesis when laminectomy was performed.[34] However, in a study of a case series of 20 adult patients, no correlation was found between the thoracolumbar kyphotic angle or size of the spinal canal and outcomes surgical decompression with laminectomy.[15]

Overall, the post-operative complications rate can reach up to 40%, while subsequent surgery can reach up to 50%.[13]

Study limitations:

The suitable articles included for the purposes of this review originated mainly from 2 centres (USA, Netherlands). The potential bias of dual-inclusion of patients and duplication of results could not be eliminated. All studies were retrospective review of case series and no randomised-controlled trials were available.

We compiled the available data as reported by the authors. In presence of multiple confounding factors and the heterogeneity of surgical techniques as well as reported outcomes, it is difficult to establish reliable conclusions from the analysis of a small number of included studies. The number of analysable outcome measures was also smaller than anticipated due to a paucity of studies reporting certain events.

The lack of high-quality data would not qualify for a formal meta-analysis. Nonetheless, we still believe the findings of this literature review are important in highlighting the gaps and deficiencies in the available evidence and offer an insight to the necessity of higher quality studies to address this.

Our search was limited to the English literature and studies available in full text, which has an inherent bias with regards to the limitation of number of studies included, as well as, the publication bias which has tendency not to publish literature that may contain negative or neutral results. Moreover, two out of five studies included in this review had the same senior author, [20,22] which could represent an overlap between studies and potentially same patients included in both studies and therefore duplication of some of the data analysed.

Conclusions:

This study highlights the outcomes of surgical treatment of spinal stenosis in adult achondroplasia patients and differences from the paediatric group. Whilst surgical decompression with or without instrumentation can improve patients' symptoms, function and level of independence, the duration of symptoms prior to surgical intervention seems to play an important role in determining the response to surgical treatment. In contrast to the paediatric group, in adults, the indications for instrumentation are less clear and should be considered for each case on its own merit.

Overall, surgical decompression of spinal stenosis with or without instrumented stabilisation is associated with significant overall risk of complications and revision surgery in both groups. Instrumented stabilisation appears to have clear role in the paediatric group to avoid post-operative spinal deformity.

Achondroplasia patients should be educated with regards to symptoms associated with spinal stenosis, and encouraged to seek medical advice at an early stage to have the best chance of recovery and maintaining their function. When surgery is required, those patients should be informed of the high rate of potential complications that can be associated with their surgical treatment. Multi-centre results with less variation in reporting outcomes using national or international registries might offer a better foundation for further high-quality research and better understanding of such a rare condition in this specific group of patients.

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ABSTRACT

Background: This study aims to assess the quantity and quality of available literature on surgical treatment outcomes of spinal stenosis in adult and paediatric achondroplasia patients through a systematic review of literature and to investigate the suitability of conducting a meta-analysis on outcomes of surgical treatment.

Methods: Online databases were searched according to PRISMA guidelines. No restrictions regarding study design, sample size, previous treatment, or publication date were implemented. The following terms: "Spinal stenosis", "Spinal Decompression", "Spinal fusion", each term separately combined with the term "Achondroplasia" were used. Quality of the included studies were assessed used the Modified Coleman method.

Results: Five adult and four paediatric single-sample non-comparative studies were identified for inclusion (176 adult and 102 paediatric patients). Meta-analyses assessed the proportion of patients achieving full resolution of symptoms to be 0.51 (95% CI 0.00 to 1.00); the proportion of patients achieving full or partial resolution of symptoms to be 0.90 (95% CI 0.84 to 0.97); the proportion of procedures requiring re-operation to be 0.42 (95% CI 0.34 to 0.50; and the proportion of procedures involving dural tears to be 0.20 (95% CI 0.02 to 0.39). Statistical heterogeneity was very high for full resolution of symptoms and requirement for dural repair; and very low for other outcomes.

Conclusions: The available literature on this population and condition is sparse, highly heterogenous, and is generally of low quality limiting the value of meta-analysis. Overall, outcomes of surgical decompression of symptomatic spinal stenosis in achondroplasia patients show consistent degree of resolution of symptoms. Duration of symptoms prior to surgical treatment appears to play an important role in the overall outcome of treatment. Therefore, a delay in diagnosis and treatment can potentially be detrimental in achieving a better outcome.

Keywords: Achondroplasia; Stenosis; Spine; Adults; Paediatrics

INTRODUCTION

Achondroplasia, an autosomal-dominant condition with up to 80% of cases being a result of new sporadic gene mutation, is the most common form of skeletal dysplasia and the commonest type of dwarfism. This condition occurs due to a characteristic mutation in the gene encoding fibroblast growth factor receptor 3 (FGFR3) that results in inhibition of chondrocyte proliferation in the proliferative zone of the physis. [1,2]

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Dwarfism, macrocephaly, frontal bossing, rhizomelic shortening of the extremities, and other skeletal abnormalities characterize achondroplasia.[3–6] Despite their musculoskeletal abnormalities, achondroplasia individuals have normal intellectual function. [2]

Neurological problems are frequent, and can be associated with significant functional limitations, and reduction in quality of life. This can be in many forms including delayed motor development, hydrocephalus, upper cervical cord compression, and spinal stenosis.

During *in utero* spine development, achondroplasia causes impaired longitudinal growth of the posterior arches due to a disorder in enchondral ossification which results in early fusion of the pedicles to vertebral bodies, accounting for shortened pedicles. The cross-sectional area of the spinal canal is consequently narrowed by the short pedicles and reduced interpedicular distance leaving reduced space available for the neural elements that eventually can lead to nerve root compression and spinal stenosis.[5,10–14]

Although narrowing in the lumbar spinal canal occurs in all achondroplastic spines, the incidence of developing neurological symptoms is variable and has been reported by different authors to range between 20-78% [2,15], with an estimated one third of the symptomatic population to require surgical intervention.

The purpose of this systematic review was to assess the quality and quantity of available published literature on spinal stenosis in adult and paediatric achondroplasia patients, and the explore suitability of conducting a meta-analysis on the outcomes of surgical treatment of spinal stenosis in this group of patients. Furthermore, we aim to compare the outcomes in terms of success of treatment, severity and frequency of complications encountered in adult and paediatric populations.

METHODS

A systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using the online databases Medline/Pubmed, The Cochrane Library, EMBASE, AMED, and CINAHL. Articles were identified using an electronic search of the following keyword terms: “Spinal stenosis”, “Spinal Decompression”, “Spinal fusion”, each term separately combined with the term “Achondroplasia”.

To be included, studies needed to be fully published in English language and reporting the results of one or more surgical treatment option for spinal stenosis in adult or paediatric Achondroplasia patients. There were no restrictions regarding study design, population size, previous treatment, intensity or duration of symptoms, or publication date.
We excluded case reports, morphometric, and technique comparative studies.

Data from each included study was extracted. The following information was recorded: age, follow-up duration, duration of symptoms, symptoms (motor and/or sensory deficits, neurogenic claudication, radicular pain, bowel and/or bladder dysfunction), previous surgery, type of procedure, patient reported outcomes, resolution of symptoms (full, partial, none), re-operation, type of consequent surgery if any, interval time to re-operation, complications (dura tear, kyphotic deformity, deep infection, wrong level decompression) and return to work if applicable.

To assess the quality of the studies included in our review, two independent authors (ZA, BL) used the Modified Coleman Methodology which results in a score between 0 and 100.[17,18] In our data analysis, when an outcome measure was not reported by the authors, their cohort was excluded from our statistical analysis for that specific outcome to avoid making any assumptions.

Meta-analyses methods

Single-proportion random effects meta-analyses were conducted on the following outcomes: full resolution of symptoms; full/partial resolution of symptoms; re-operation; dura tear. Meta-analyses were not conducted on other measured outcomes (post-operative kyphosis; deep infection, wrong level) due to these events being recorded at non-zero levels in only one study each. All meta-analyses conducted used the number of patients as the denominator.

In each meta-analysis, a synthesised estimate for the proportion of patients or procedures associated with the event of interest, with an associated 95% confidence interval (CI) was derived. A *Z*-test for overall effect was also conducted and reported. Heterogeneity was assessed using Cochran's Q test, the I^2 statistic and the τ^2 statistic (between-study variance). Statistical analysis was conducted using Stata statistical software Version I/C 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). All results were summarised in tabulated form and in forest plots.

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RESULTS

In total, 327 articles were retrieved through the primary search. The articles were screened by title and abstract for relevance. A total of 42 articles were found to be of relevance to the subject of the study. The full text was retrieved for further analysis of the aforementioned studies. Following application of the exclusion and inclusion criteria, 9 articles suitable for the purposes of this systematic review remained. Five studies were focused on adults and the other four were concerned with paediatric population of patients. The vast difference between adults and paediatrics regarding the anatomy and physiology of their skeleton dictated us to interpret and report the results of each population separately.

Figure 1. Flowchart illustrating the selection of articles included in the review

The average Modified Coleman Methodology score for adult studies was 41.6 versus 37.7 out of 100 for paediatric studies.

The total number of patients in the adult cohorts was 176 patients with an average age of 39.9 years, and 102 patients from the paediatric cohorts with an average age of 11.8 years. In adults, patient follow-up ranged between the included studies from 1 to 25 years, while in the paediatric studies it ranged from 8 months to 8.3 years. Lumbar spine, followed by thoraco-lumbar were the most common operated segments of spine in both adult and paediatric cohorts.

Adults Results

The average duration of symptoms was reported in 4 out of 5 studies and was 4 years and 9 months prior to treatment. Patients were reported to have variable symptoms, with neurogenic claudication being the most common presenting symptom reported in 57% of adult patients. Sensory and motor deficit were reported in 30% and 15% of patients respectively, while bladder and/or bowel dysfunction was present in 32% of patients.

Three out of five studies reported a total of 2~~2~~64 patients out of 105 (~~22~~25%) to have documented previous spine surgery prior to their intervention.[19, 21, 23~~13, 14~~,19]

Whilst most patients in the adult group underwent decompression of spinal stenosis without instrumentation, 5 (3%) patients required instrumented fusion in addition to decompression.

Table 1. Adult Patients' characteristics and intervention

Table 2. Adults - Outcomes and complications

When resolution of symptoms following surgical intervention was reported, full resolution was observed in 54% of patients, whilst 37% had partial resolution, and 9% showed no improvement in their pre-operative symptoms.

Pyreitz et al reported 2 out of 20 patients with no improvement in neurological symptoms. One patient developed paraplegia following second laminectomy which persisted despite third attempt to release compression. [20 19]Thomeer et al reported one case of deteriorating neurological status with diminished bladder

control which was secondary epidural haematoma. [19,20] Vleggeert-Lankamp et al reported 3 cases that failed to demonstrate neurological improvement to wrong-level operation. [21]

As demonstrated in table (2), Patient Reported Outcomes (PROMs) were reported in three studies.[20–22] Odom criteria analysis of the patient outcome scores showed that in a study of 20 patients, 25% showed no change or worsening in their symptoms postoperatively, while 75% had partial or full resolution of their symptoms. In the same study, functional status was observed to improve by 1 point on the Cooper scale in 8 out of 20 patients (40%), while 12 out of 20 patients (60%) maintained same level of function post-operatively. No cases showed deterioration in function.[21]

The overall walking distance improved post-operatively as demonstrated in a study of 49 patients. This seemed to be strongly correlated with the duration of symptoms pre-operatively. Patients with symptom duration of less than 6 months before their first laminectomy (14 out of 49 participants [28.6%]) had 7 times better chance to experience improvement in walking distance and were 4 times more likely to experience a decrease by at least one full Rankin level than those who had had symptoms for greater than 6 months, reflecting greater independence.[20]

The reported post-operative complications are demonstrated in Table (2). The rate of re-operation for any complication, recurrence of symptoms or failure to resolve symptoms was 44%, while intra-operative dura tear occurred in 36% of patients.
Post-operative kyphotic deformity was noted in 2 patients only, and deep infection in 4 patients, whilst 3 patients underwent surgical intervention at the wrong spine level.

Adult Meta-analysis results

The estimates extracted from each of the meta analyses conducted on the included adult studies is summarised in Table (3) and Figures (2-5) below.

Table (3). Adults - summary of meta-analysis parameters

Pyeritz et al. (1987) reported in their case series promising results in the first 6 months of follow-up, with high rate of return of bladder function and muscle strength provided decompression occurred within few weeks of symptoms onset or deterioration. However, the long-term results were mixed, and the authors noticed that narrow laminectomy was associated with a high rate of re-stenosis (41%) and post-operative hypertrophic scarring at one or more levels of the original laminectomy. The authors reported that 2 out of 22 (9%) patients in this cohort underwent fusion secondary to developing post-operative kyphotic deformity.[23]

A study of 36 cases who were treated with widening lumbar interapophyseolaminar diameter without laminectomy reported full resolution of symptoms in 71% of patients, while 23% remained with tolerable symptoms and 6% had no benefit from surgery. However, 14 out of 36 (39%) patients required further surgical interventions due to inadequate relief of symptoms. There was no mention by the authors of how many procedures performed in the group of patients who had full resolution of symptoms initially. [19]

Figure 2. Forest plot for meta-analysis assessing proportion of adult patients experiencing full resolution of symptoms

Figure 3. Forest plot for meta-analysis assessing proportion of adult patients experiencing full/partial resolution of symptoms

In a retrospective study of 8 patients who had clinically significant re-stenosis at previously decompressed levels, instability was identified in 4 patients (50%) due to previous facetectomy or extensive foraminotomy. Two patients had no pre-operative kyphosis and were treated with transverse process fusion and external orthosis, while the other two (25%) had kyphotic deformity and required fusion with instrumentation. [24]

Figure 4. Forest plot for meta-analysis assessing proportion of procedures requiring re-operation in adults

Figure 5. Forest plot for meta-analysis assessing proportion of procedures involving dura tear in adults

Paediatrics Results

In the paediatric cohorts, two-thirds of the patients were found to have motor weakness, neurogenic claudication and sensory deficit, while less than half were reported to have bladder or bowel dysfunction. The least common symptom was radicular pain, reported in nearly 1 out of 5 patients. As reported in three studies[25–27], 26 out of 92 patients (28%) had had previous spine surgery. Out of 118 procedures, 70% included instrumented fusion.

Table 4. Paediatric patients' characteristics and intervention

None of the studies included a patient-reported or functional outcome tool to report the outcome of their intervention.

Full resolution of symptoms was reported in 46/72 (67%) of patients, whilst 25% experienced partial resolution, and 8% had no improvement. Revision surgery was required in 20 out 72 (28%) of patients.

Bydon et al reported statistically significant resolution of neurogenic symptoms in all their patients compared to the baseline status following surgical intervention with neurogenic claudication, weakness, and radiculopathy showing complete resolution. [25,] Baca et al reported improvement in claudication, weakness, numbness, incontinence, and abnormal reflexes in 61%, 56%, 50%, 72% and 33% of their patients respectively. Three out of 18 patients (16%) developed new onset neurologic symptoms with 2 patients showing new-onset weakness and 1 patient with new-onset abnormal reflexes. [27] Sciubba et al reported persistence of myelopathic symptoms in 1 patient despite adequate decompression and no evidence of stenosis at different level on MRI and new-onset radiculopathy in 3 patients, two of which were treated conservatively and one patient underwent repositioning of pedicle screw with resolution of symptoms afterwards.[26]

In the combined results of all studies, the most common encountered complication recorded post-operatively was the development of spine kyphotic deformity. This was reported in 24 out of 102 patients (23.5%); followed by intra-operative dural tear, which occurred in 18 out of 92 (20%) patients. Deep infection was reported in 2 studies and affected 5 out 77 patients (6.5%), while no patients underwent surgical intervention at the wrong level.

Table 5. Paediatrics - Outcomes and complications

Paediatrics Meta-analysis Results

The estimates extracted from each of the meta analyses conducted on the included studies is summarised in Table 6 and figures 6-9 below.

Figure 6. Meta-analysis summary of proportion of paediatric patients experiencing full resolution of symptoms.

Figure 7. Meta-analysis summary of proportion of paediatric patients experiencing full or partial resolution of symptoms

In a retrospective study of 44 paediatric patients with an average age of 12.7 years who underwent a total of 60 surgical decompression procedures, 43 (72%) procedures involved instrumented fusion and autograft, revision surgery was required in 11 (25%) cases. [26]

In 2010, another study including 18 paediatric patients of which 9 patients were skeletally immature (Risser grade <5) and received instrumentation in addition to decompression, revision surgery was required by 9 (50%) of the cases. Seven out of nine (78%) revision cases were for patients who underwent decompression without instrumentation. All revisions were due to progressive and symptomatic kyphotic deformity with abnormal sagittal profile that required instrumentation.[27]

Figure 8. Forest plot for meta-analysis assessing proportion of procedures requiring re-operation in paediatrics

A meta-analysis of dural tear in paediatrics demonstrated in figure (9) was reported in 3 studies.[25–27] Between the studies, intra-operative dural tears ranged from 6-40%.

Figure 9. Forest plot for meta-analysis assessing proportion of procedures involving dura tear in paediatrics

DISCUSSION

This study analysed the available literature on achondroplasia patients who were treated surgically for spinal stenosis. To our knowledge, there has been no previous systematic reviews on this condition and group of patients published in literature.

Our review demonstrated that the quantity of literature available on this topic is limited and of overall low quality. In addition, the high heterogeneity and variability in reporting outcomes between the studies made the results of a meta-analysis not reliable to draw conclusions.

The results of our review showed that the outcomes of surgical decompression for spinal stenosis in adults and paediatrics with achondroplasia are favourable with regards to resolution of symptoms, improvement in function and greater independence and patients who presented within 6 months from the onset of their symptoms appeared to have better results. Nonetheless, surgical treatment of spinal stenosis in this unique group of patients can be associated with significant risks of intra- and post-operative complications that must be acknowledged in the process of counselling and consenting of patients offered surgery. Recurrence of stenosis, at the same site or junctional, was a common complication encountered that often lead to repeated surgical interventions and further decompressions which expectedly showed a higher risk of complication, as well as, a risk of spinal destabilisation when more levels were decompressed. In skeletally immature achondroplastic patients, there is significant potential advantage in favour of instrumented stabilisation over decompression alone in order to prevent the development of spinal deformity.

Resolution of symptoms

In the general population with degenerative spinal stenosis, good surgical results have been reported in 68% of patients after a mean follow-up period of 12 years.[28,29] Despite this, up to 20% of patients undergoing primary surgery for spinal stenosis do not experience sustained symptomatic pain relief.[30]

In our comparison of the adult achondroplasia results to the paediatric group with regards to resolution of symptoms, we found that spinal decompression had a similar success rate in resolving symptoms as revealed by the meta-analyses, and the synthesised estimates for the outcome measures were broadly comparable to

those generated from a parallel analysis of paediatric patients. The proportion of adult patients estimated to experience full or partial resolution of symptoms, at 0.90 was in fact identical to the corresponding figure derived in the parallel paediatric study, which also generated an estimate of 0.66 for the proportion of paediatric patients estimated to experience full resolution of symptoms.

Risk of re-operation

On the other hand, the estimates of re-operation and dura-tear occurrence in the study of adult patients (0.42 and 0.20) were also almost identical to the corresponding estimates in the study of paediatric patients (0.42 and 0.18).

In adults, the re-operation rate reported by different authors ranged from 25%-45%, which is slightly less than but comparable to what we found in the paediatric group of patients that ranged from 25-100% between studies. Whilst post-operative spinal deformity, mostly kyphotic, was the main reason for re-operation in children, in adults, recurrence of stenosis seemed to be the most common reason for re-operation. Recurrence of stenosis in the previously decompressed spine might be attributed to accelerated facet hypertrophy, bony overgrowth and scarring. The accelerated hypertrophy may represent instability in the previously decompressed achondroplastic spine or some exaggerated response to normal motion resulting from the genetic defect of this condition.[24] The~~is~~ variation in rate of re-operation in the paediatric group might be explained by the results of 10 skeletally immature achondroplasia patients with an average age of 9.2 years who underwent multilevel thoracolumbar laminectomies of 5-8 levels and demonstrated a 100% progressive postoperative thoracolumbar kyphosis (mean 94°, range 78°-135°). All patients underwent a second procedure and instrumentation was performed at an average of 13.2 months from the primary procedure.[31] Those results from a single study might skew and overestimate the actual rate of revision or re-operation in the paediatric group overall. Equally, the outcomes of this particular study is of significance as it demonstrated the potential significant importance of using instrumentation in the growing spine, an observation that is not felt to be similar significance in the adult group.

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Progressive spinal deformity

Post-operative spine progressive deformity in children was a frequently observed outcome when primary spinal decompression was performed without instrumented stabilisation. In one study, this was reported in 100% of the patients.[31] However, a similar outcome was not observed in the adult population. In contrast to children, post-operative deformity was reported in one adult study, affecting 2 out of 22 (9%) patients only.[23] Several reasons can be attributed to this. The anatomical difference between children and adults, mainly represented by the ongoing axial and peripheral skeletal growth in children, providing a dynamic environment in contrast to the static environment found in a skeletally mature adult. Nonetheless, multiple other factors must also be taken into consideration, and that includes the number of levels decompressed in each case, as well as, the method of decompression. Also, the possibility of under reporting by authors in the adult studies, and the difference in follow-up time between studies, are all factors that could potentially mask the true incidence of post-operative deformity in adults.

Dural tear

Intra-operative dural tear incidence was highly variable in general. In the adult group, it ranged between 5-55% of cases, while in the paediatric group, it ranged from 6% to 40%. In comparison, the incidence of dural tear in general non-achondroplasia patients with spinal stenosis appear to be lower, with incidental durotomy rates in the published literature ranging from 3.5% for primary discectomy and 13.2% for revision discectomy in adult populations,[32] with 0.34% in index procedures and up to 18.5% in revision operations in paediatric populations.[33] The reason for this increased risk of dural tear in Achondroplasia might be secondary to intrinsic, non-modifiable risk factors. These include anatomic sequelae of the underlying dysplasia, such as severity or chronicity of congenital stenosis, increased lumbar lordosis, horizontal positioning of the sacrum, and increased thoracolumbar kyphosis, which may predispose this unique group of patients to this complication. [34]

Comparing ultrasonic bone curette (BoneScalpel) in 10 patients versus high-speed drill in 20 patients in a retrospective review of 30 paediatric achondroplastic patients who were treated for spinal stenosis using showed a decreased number of durotomies and overall complications in the ultrasonic bone curette

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(BoneScalpel) cohort versus the high-speed drill cohort. Those results originate from a single study with small number of patients, therefore definitive conclusions cannot be made about the superiority and protective effect of the ultrasonic bone curette device over the high-speed drill.

Neurological recovery

The recovery of neurological symptoms such as neurogenic claudication, weakness, numbness, incontinence or abnormal reflexes was variably reported between studies.

Across all studies reporting on the neurological status post-operatively, the majority of patients showed improvement in their symptoms with variable degree of sustainability. In the early post-operative phase, in cases where no improvement is observed or new onset neurological deficit is noticed, further investigations are warranted to rule out the possibility of wrong level surgery or suboptimal positioning of pedicle screws when used. In the longer term, recurrence of stenosis or junctional stenosis should be considered and investigated, especially in when symptoms are not tolerated by patients.

The body mass index (BMI), duration of symptoms, time to surgery and degree of pre-operative kyphotic deformity were amongst other factors studied in the literature.

In a study of 49 patients, the body mass index (BMI) was found to have no significant effect on the functional and surgical outcomes including: walking distance, intra- or post-operative complications, and subsequent revision laminectomy.[22]

In thoracic spine, a kyphotic angle greater than 40° was suggested to be the threshold for spondylodesis when laminectomy was performed.[34] However, in a study of a case series of 20 adult patients, no correlation was found between the thoracolumbar kyphotic angle or size of the spinal canal and outcomes surgical decompression with laminectomy.[15]

Overall, the post-operative complications rate can reach up to 40%, while subsequent surgery can reach up to 50%.[13]

Study limitations:

The suitable articles included for the purposes of this review originated mainly from 2 centres (USA, Netherlands). The potential bias of dual-inclusion of patients and duplication of results could not be eliminated. All studies were retrospective review of case series and no randomised-controlled trials were available.

We compiled the available data as reported by the authors. In presence of multiple confounding factors and the heterogeneity of surgical techniques as well as reported outcomes, it is difficult to establish reliable conclusions from the analysis of a small number of included studies. The number of analysable outcome measures was also smaller than anticipated due to a paucity of studies reporting certain events.

The lack of high-quality data would not qualify for a formal meta-analysis. Nonetheless, we still believe the findings of this literature review are important in highlighting the gaps and deficiencies in the available evidence and offer an insight to the necessity of higher quality studies to address this.

Our search was limited to the English literature and studies available in full text, which has an inherent bias with regards to the limitation of number of studies included, as well as, the publication bias which has tendency not to publish literature that may contain negative or neutral results. Moreover, two out of five studies included in this review had the same senior author, [20,22] which could represent an overlap between studies and potentially same patients included in both studies and therefore duplication of some of the data analysed.

Conclusions:

This study highlights the outcomes of surgical treatment of spinal stenosis in adult achondroplasia patients and differences from the paediatric group. Whilst surgical decompression with or without instrumentation can improve patients' symptoms, function and level of independence, the duration of symptoms prior to surgical intervention seems to play an important role in determining the response to surgical treatment. In contrast to the paediatric group, in adults, the indications for instrumentation are less clear and should be considered for each case on its own merit.

Overall, surgical decompression of spinal stenosis with or without instrumented stabilisation is associated with significant overall risk of complications and revision surgery in both groups. Instrumented stabilisation appears to have clear role in the paediatric group to avoid post-operative spinal deformity.

Achondroplasia patients should be educated with regards to symptoms associated with spinal stenosis, and encouraged to seek medical advice at an early stage to have the best chance of recovery and maintaining their function. When surgery is required, those patients should be informed of the high rate of potential complications that can be associated with their surgical treatment. Multi-centre results with less variation in reporting outcomes using national or international registries might offer a better foundation for further high-quality research and better understanding of such a rare condition in this specific group of patients.

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