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Reporting of Randomised Clinical Trials in Skull Base Surgery: A Fourteen-Year Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SA and JH designed the study. Authors AN and MN wrote the protocol, and wrote the first draft of the manuscript. Authors AN and MN managed the literature searches and analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Skull base surgery has experienced dramatic advances in the last decade. Recently, various surgical disciplines have conducted reviews of quality of randomised controlled trials (RCTs). This is the first review to our knowledge regarding RCT quality within skull base surgery.
Systematic review of skull base surgery RCTs published between 2000 and 2014 were conducted. Literature search provided 96 papers. Duplicates and trials which did not meet our inclusion criteria were excluded. This left 28 papers for analysis. A total of 1785 patients participated across trials.
Consolidated Standards of Reporting Trials statement (CONSORT) and Jadad scale were used assess to the quality of reporting. These were our main outcome measures.

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The mean CONSORT score prior to 2011 was 16.9 (n = 17, range; 13 – 22), and post 2011 was 17.5 (n = 11, range; 12 – 22). The mean Jadad score was 3.1 (n = 28, range 2 – 5). CONSORT were found to increase significantly with both increasing sample size (rho=0.467, p=0.012) and Jadad scores (rho=0.540, p=0.003). Linear regression showed CONSORT increase by 0.36 (95% CI: 0.02 – 0.70, p=0.041) for each additional 10 patients included, and by 1.50 (95% CI: 0.58 – 0.24, p=0.002) for each increase of one in the JADAD score.
There are common omissions related to randomization, sample size calculations and availability of protocols. RCTs in skull base surgery are comparable to other surgical disciplines. We recommend utilisation of the CONSORT statement during protocol formation of RCTs to improve reporting of trials.

Keywords: Skull base; CONSORT; Jadad; pituitary; endonasal endoscopic; randomised controlled trials.

1. INTRODUCTION

Properly conducted trials, following scientific platforms are widely accepted as the foundations of treatment efficacy and safety [1]. The importance of such trials is that evaluation of a smaller population, where outcome of treatment variability is analysed, can effectively influence the management of the general population in the future. Retrospective trials contain serious potential bias, which could potentially influence outcomes. As a result it is accepted that the gold standard for clinical investigations is the randomised controlled trial (RCT), however these are not without controversy, especially in surgical disciplines where it may be difficult or even unethical to randomise to a non-surgical treatment arm.

RCT reporting should transparently convey the design, conduct, analysis and learning points [2]. Despite this, RCTs are still not being reported adequately [3-5]. Poor reporting can create difficult interpretation and application.[3] On account of this, an international group of clinical trialists, statisticians, epidemiologists and biomedical editors created the original CONSORT (Consolidated Standards of Reporting Trials) statement [4]. This was a checklist and flow diagram published in 1995, with a revision produced in 2001 [4,5] The 22 item revised checklist and 4 stage flow diagram (enrolment, intervention, allocation, follow-up and analaysis) served to reduce ambiguity regarding design and reporting of RCTs, enabling readers to understand the trial's conduct and assess results.[5,6] Data highlighted its use in improvement of quality of RCT reports, with usefulness dictated by continuous biomedical literature [6-8]. The CONSORT statement was further revised in 2010, extending the checklist to 25 items (Table 1) [9]. The Jadad scale is a similar tool used to assess effectiveness of randomised controlled trials using a three item system, resulting in a score from 0 (low-quality study) to 5 (high-quality study) (Table 2). It has been found to contain many of the important elements that have empirically been shown to correlate with bias and it has known reliability and external validity [10].

Reviews of RCT reporting within various surgical specialities, including paediatric, general and trauma surgery highlights multiple weaknesses resulting in a lack of transparency of reporting [11-13].

Having first been described in the late nineteenth and early twentieth centuries, skull base surgery has experienced dramatic advances over the last decade [14]. This includes advances in surgical technique, neuronavigation and optics, as well as involvement of specialities outside of neurosurgery [15]. As a result, there is an understandable groundswell of interest with appropriate research within this domain. We aim to utilise the CONSORT guidelines and Jadad scale to assess the quality of reporting, whilst simultaneously highlighting areas of research, and revealing future aspects of skull base surgery yet to be subjected to RCT. This is highly relevant within an age of evidence based medicine, owing to the importance of the quality of data collection and reporting. The aim of this paper is to analyse previous trials and provide a platform for effective future trials. To our knowledge there is no such paper analysing the strength of skull base surgery reporting. It is important to provide this information to assess the reliability of the data we provide within different surgical disciplines.

Table 1. Changes to original CONSORT statement 9

Item 1b (title and abstract)	We added a sub-item on providing a structured summary of trial design, methods, results and conclusions and referents the CONSORT for abstracts article
Item 2b (introduction)	We added a new sub-item (formerly item 5 in CONSORT 2001) on “Specific objectives or hypotheses”
Item 3a (trial design)	We added a new item including this sub-item to clarify the basic trial design (such as parallel group, crossover, cluster) and the allocation ratio
Item 3b (trial design)	We added a new sub-item that addresses any important changes to methods after trial commencement, with a discussion of reasons
Item 4 (participants)	Formerly item 3 in CONSORT 2001
Item 5 (interventions)	Formerly item 4 in CONSORT 2001. We encouraged greater specificity by stating that descriptions of interventions should include “sufficient details to allow replication”
Iteam 6 (outcomes)	We added a sub-item on identifying any changes to the primary and secondary outcome (endpoint) measures after the trial started. This followed from empirical evidence that authors frequently provide analyses of outcomes in their published papers that were not the pre-specified primary and secondary outcomes in their protocols while ignoring their pre-specified outcomes (that is, selective outcome reporting). We eliminated text on any methods used to enhance the quality of measurements
Item 9 (allocation concealment mechanism)	We reworded this to included mechanism in both the report topic and the descriptor to reinforce that authors should report the actual steps taken to ensure allocation concealment rather than simply report imprecise, perhaps banal, assurances of concealment
Item 11 (blinding)	We added the specification of how blinding was done and, if relevant, a description of the similarity of interventions and procedures. We also eliminated text on “how the success of blinding (masking) was assessed” because of a lack of empirical evidence supporting the practice as well as theoretical concerns about the validity of any such assessment
Item 12a (statistical methods)	We added that statistical methods should also be provided for analysis of secondary outcomes
Sub-item 14b (recruitment)	Based on empirical research, we added a sub-item on “Why the trial ended or was stopped”
Item 15 (baseline data)	We specified “A table” to clarify the baseline and clinical characteristics of each group are most clearly expressed in a table
Item 16 (numbers analysed)	We replaced the mention of “intention to treat” analysis, a widely misused term, by a more explicit request for information about retaining participants in their original assigned groups
Sub-item 17b (outcomes and estimation)	For appropriate clinical interpretability, prevailing experience suggested the addition of “For binary outcomes, presentation of both relative and absolute effect sizes is recommended”
Item 19 (harms)	We included a reference to the CONSORT paper on harms
Item 20 (limitations)	We changed the topic from “interpretation” and supplanted the prior text with a sentence focusing on the reporting of sources of potential bias and imprecision
Item 22 (interpretation)	We changed the topic from “Overall evidence”. Indeed, we understand that authors should be allowed leeway for interpretation under this nebulous heading. However, the CONSORT Group expressed concerns that conclusions in papers frequently misrepresented the actual analytical results and that harms were ignored or marginalized. Therefore, we changed the checklist item to include the concepts of results matching interpretations and of benefits being balanced with harms
Item 23	We added a new item on trial registration. Empirical evidence supports the

(registration)	need for trial registration, and recent requirements by journal editors have fostered compliance
Item 24 (protocol)	We added a new item on availability of the trial protocol. Empirical avidence suggests that authors often ignore, in the conduct and reporting of their trial, what they stated in the protocol. Hence, availability of the protocol can instigate adherence to the protocol before publication and facilitate assessment of adherence after publication
Item 25 (funding)	We added a new item on funding. Empirical evidence points toward funding source sometimes being associated with estimated treatment effects.

Table 2. Jadad scale

Item	Maximum points	Description
Randomization	2	1 point if randomization mentioned 1 additional point if the method of randomization is appropriate Deduct 1 point if the method of randomization is inappropriate (minimum 0)
Blinding	2	1 point if blinding is mentioned 1 additional point if the method of blinding is appropriate Deduct 1 point if the method of blinding is inappropriate (minimum 0)
An account of all patients	1	The fate of all patients in the trial is known. If there are no data, the reason is stated

2. METHODOLOGY

2.1 Search Strategy

The data within this paper is supported by a systematic literature review using MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials. The search included the key words (skull base) OR (pituitary) OR (acromegaly) OR (cushing) OR (transphenoidal) OR (endoscopic endonasal) OR (meningioma). We limited the search to including only human trials, published in English between 01/01/2000 to 31/11/2014.

2.2 Inclusion/Exclusion Criteria

The full inclusion and exclusion criteria is summarised in Table 3. Articles were included if they assessed a living human population with any skull base disease, using a prospective Randomised Controlled Trial between 01/01/2000 to 31/11/2014, with access to the full article in English. All other articles were excluded.

A subsequent level of screening excluded duplicate articles, and publications not related to skull base surgery, such as endocrinology of the HPA axis, pregnancy and in-vitro fertilisation (IVF) treatment.

2.3 Method and Data Analysis

All papers which adhered to our inclusion and exclusion criteria were obtained in full and were subsequently appraised using the CONSORT statement and the Jadad scale by two independent observers. Further data from each paper were extracted including; number of authors, location of study, methodology, number of patients, year of publication and synopsis of study. These factors were divided into two classes, those that were ordinal or continuous, and those that were categorical. Comparisons between ordinal or continuous variables were made using Spearman's correlation coefficients, with linear regression models produced where significant associations were found.

Ordinal and continuous variables were then compared across categorical variables using Mann-Whitney or Kruskal-Wallis tests, as appropriate, with medians and ranges used as summary statistics. Where Kruskal-Wallis tests returned significant results, post hoc comparisons between all groups were made using Mann-Whitney tests, with the p-values Bonferroni corrected for the number of comparisons being made.

Finally, comparisons between categorical variables were made using Fisher's exact test. All analyses were performed using IBM SPSS Statistics 22 (IBM Corp. Armonk, NY), with $p<0.05$ deemed to be indicative of statistical significance.

Table 3. Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
Patients with any skull base condition	Non-skull base related conditions
Human participants	Non-human participants, cadavers
Prospective randomised controlled trial	Retrospective non-randomised trial
Full journal article available	Abstracts
Trial related directly to management of skull base condition	Related to conditions outside of skull base
Published between 01/01/2000 to 31/11/2014	Published outside of date range
Produced in English	Foreign language
Published within MEDLINE, EMBASE and Cochrane Central Register of controlled trials	Published outside of MEDLINE, EMBASE and Cochrane central register of controlled trials

3. RESULTS

3.1 Study Selection

A combination of the key words aforementioned provided 96 papers using all databases. Duplicates were subsequently excluded leaving 73. Papers that were non-human, written in a foreign language, cadaver based and did not meet our inclusion criteria were also excluded. This left a total of 28 (Fig. 1 and Table 4) [16-43].

A total of 1785 patients participated across all RCTs matching our inclusion and exclusion criteria between 2000 and 2014. The mean number of authors was 6.7 (range; 2^{41} – 13^{17}), when considering only named authors in collaborative studies. Approximately half of the studies were performed in Europe [16,17,21,24,25,26,30,32,34,36,38,39,42], with Italy and China producing the highest quantities of studies nationally; 5/28 each respectively (Fig. 2). There were no RCTs produced outside of Europe, Asia and North America. The impact factor of journals ranged from 0.947^{33} to 6.310^{18} in 26 journals, whilst Surgical Neurology was discontinued and therefore did not receive a 2013 impact factor. The median impact factor was 2.347. Over half the studies were published in the last five years, ranging between 1 and 6 yearly.

All studies were prospective in nature. Blinding of participants, observers or surgeons occurred in 11 studies, whilst 4 used a placebo. There were a total of 3 double blinded, randomised controlled trials designed during the study period. These related to pre-operative medical treatment, peri-operative haemostasis control and post-operative analgesia. 13 of the studies investigated acromegaly, whilst other areas including meningioma, prolactinoma, craniopharyngioma and pituitary adenoma. 8 studies did not address a specific condition, investigating any lesion within the skull base (Fig. 2).

3.2 Data Analysis

The mean CONSORT score of papers published between 2000 and 2014 was 16.9 (n = 17, range; 13 – 22), and from 2011 onwards was 17.5 (n = 11, range; 12 – 22). The mean Jadad score was 3.1 (n = 28, range 2 – 5). With regards to topics of investigation a majority (36%) related to peri-operative management, with less than half addressing surgical technique (Fig. 2).

Data were available for a total of 28 studies. The data were complete in all parameters being measured, with the exception of the impact factor, where two values were missing due to the journals being discontinued. Since the CONSORT guidelines changed in 2010, the analysis was performed separately using both versions. However, since the two guidelines were so similar (rho=0.967), both sets of analyses returned comparable results, and only the more recent version of CONSORT was subsequently reported throughout.

Table 5 reports the correlations between the continuous factors being considered. CONSORT scores were found to increase significantly with both increasing sample size (rho=0.467, p=0.012) and JADAD scores (rho=0.540, p=0.003). In addition to this, higher impact factors of journals were observed in RCTs with a greater number of authors (rho=0.622, p=0.001), and in the more recently published papers (rho=0.529, p=0.005).

Table 4. Summary of included papers

Author	Year of publication	Journal	Country of origin of research	Type of study	Number of patients	Synopsis of study
Fougner et al.	2014	European Journal of Endocrinology	Norway	Pre-operative	61	Pre-operative octreotide prior to surgery for acromegaly
Colao et al.	2014	Journal of Clinical Endocrinology and Metabolism	Italy	Medical treatment	358	Pasreotide vs octreotide medical treatment
Casar-boroto et al.	2013	Journal of Clinical Endocrinology and Metabolism	Norway	Pre-operative	26	Pasreotide prior to surgery
Baddour et al.	2013	International Forum of Allergy & Rhinology	USA	Peri-operative	130	Sonopet bone aspirator comparison to traditional instruments
Farag et al.	2012	International Forum of Allergy & Rhinology	USA	Post-operative	40	Surfactant comparison to hypertonic saline irrigation
Benson et al.	2012	European Journal of Endocrinology	Germany	Medical treatment	38	Glucocorticoid treatment for secondary adrenal insufficiency
Tam et al.	2012	International Forum of Allergy & Rhinology	Canada	Peri-operative	20	Olfactory outcomes with and without septal flap
Li et al.	2012	Journal of International Medical Research	China	Pre-operative	49	Pre surgical lanreotide treatment
Tutunca et al.	2012	Pituitary	Turkey	Post-operative	68	Octreotide vs lanreotide post operatively
Madsen et al.	2012	Journal of Clinical Endocrinology and Metabolism	Denmark	Medical treatment	18	Pegvisomant use in acromegaly
Karaca et al.	2011	Clinical Endocrinology	Turkey	Medical treatment	22	Octerotide-lar in comparison to surgical outcomes
Mao et al.	2010	European Journal of Endocrinology	China	Pre-operative	98	Pre surgical lanreotide treatment
Shen et al.	2010	Endocrine Journal	China	Pre-operative	39	Pre surgical octreotide treatment
Colao et al.	2009	Clinical Endocrinology	Italy	Pre-operative	81	Pre surgical octreotide treatment
Yang et al.	2009	Surgical Neurology	China	Imaging	84	Dextroscope use in imaging
Carlsen et al.	2008	Clinical Endocrinology	Norway	Pre-operative	62	Pre-operative octreotide treatment
Ali et al.	2008	Journal of Neurosurgical Aneasthesiology	India	Peri-operative	90	Propofol vs sevoflurane vs irsoflurane anaesthetic agents

Cafiero et al.	2007	European Journal of Anaesthesiology	Italy	Peri-operative	44	Remifentanil-sevoflurane Vs remifentanil-propofol anaesthetic agents
Jain et al.	2007	British Journal of Neurosurgery	India	Peri-operative	20	Endoscopic endonasal vs microscopic endonasal surgical technique
Jellish et al.	2006	Otolaryngology - Head and Neck Surgery	USA	Post-operative	120	Post-operative morphine/ondansetron vs placebo
Mishra et al.	2005	Clinical Endocrinology	UK	Medical treatment	11	Atorvastatin vs placebo crossover medical treatment
Gargiulo et al.	2003	Minerva Anestesiologica	Italy	Peri-operative	60	Remifentanil vs fentanyl use peri-operatively
Palmer et al.	2003	Journal of Neurosurgery	UK	Peri-operative	90	Aprotiin haemostasis intra-operatively
Rajaratnam et al.	2003	British Journal of Neurosurgery	India	Pre-operative	16	Pre-operative hyrdocortisone treatment
Jiang	2002	Stereotactic and Functional Neurosurgery	China	Medical treatment	19	Bleomycin treatment (3 Groups)
Cannava et al.	2001	Hormone and Metabolic Research	Italy	Medical treatment	20	Lanreotide treatment
Cho et al.	2001	Surgical Neurology	China	Peri-operative	44	Endoscopic surgery vs sublabial microsurgery
Korula et al.	2001	Journal of Neurosurgical Aneasthesiology	India	Peri-operative	57	Controlled hypercapnia vs intrathecal saline

	Number of authors	**Year**	**Impact Factor (2013)**	**Patients (N)**	**CONSORT (Post-2010)**	**JADAD**
Number of authors		0.362 (p=0.058)	0.622 (p=0.001)	0.085 (p=0.667)	0.039 (p=0.842)	-0.200 (p=0.308)
Year	0.362 (p=0.058)		0.529 (p=0.005)	0.219 (p=0.264)	0.114 (p=0.563)	-0.005 (p=0.980)
Impact factor (2013)	0.622 (p=0.001)	0.529 (p=0.005)		0.176 (p=0.390)	0.185 (p=0.365)	0.084 (p=0.682)
Patients (N)	0.085 (p=0.667)	0.219 (p=0.264)	0.176 (p=0.390)		0.467 (p=0.012)	0.283 (p=0.144)
CONSORT (Post-2010)	0.039 (p=0.842)	0.114 (p=0.563)	0.185 (p=0.365)	0.467 (p=0.012)		0.540 (p=0.003)
JADAD	-0.200 (p=0.308)	-0.005 (p=0.980)	0.084 (p=0.682)	0.283 (p=0.144)	0.540 (p=0.003)	

Table 4. Correlations between number of authors, year, impact factor of journal, number of patients, CONSORT and Jadad
Quoted coefficients are from Spearman's rho. Highlighted values are significant at p<0.05

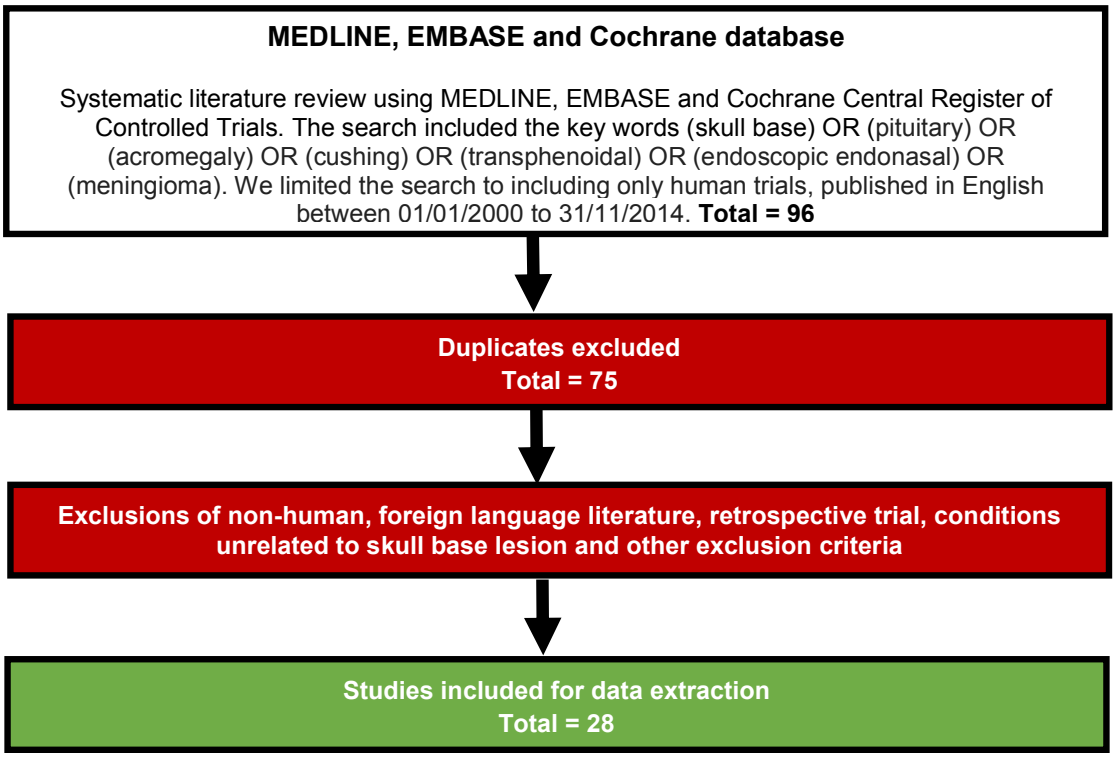

Fig. 1. Search strategy

Linear regression analysis was then performed to further quantify these relationships, the results of which are shown graphically in Fig. 3. The CONSORT score was found to increase by 0.36 (95% CI: 0.02 – 0.70, p=0.041, Fig. 3A) for each additional 10 patients included, and by 1.50 (95% CI: 0.58 – 0.24, p=0.002, Fig. 3B) for each increase of one in the JADAD score. The impact factor was found to increase by 0.34 (95% CI: 0.18 – 0.50, p<0.001, Fig. 3C) for each additional author, and by 0.17 (95% CI: 0.04 – 0.30, p=0.014, Fig. 3D) in each subsequent year of the investigation.

Table 6 reports the analysis of the categorical factors. As would be expected, studies with a placebo arm had significantly higher CONSORT (median 21 vs. 17, p=0.021) and JADAD (median 5 vs. 3, p=0.012) scores, with blinded studies also having significantly higher JADAD scores (median 4 vs. 2, p<0.001). In addition to this, both the number of authors (p=0.002) and the impact factor (p=0.003) were found to differ significantly by continent. Post-hoc analysis found that this was due to significant differences between Europe and Asia, with European papers found to have a significantly greater number of authors (median 8 vs. 5, post hoc p=0.018) and to be in significantly higher impact factor journals (median 3.35 vs. 1.75, post hoc p=0.021).

No significant differences in any of the outcomes by the type of study were detected. However, it must be noted that, due to the number of groups being compared and the small sample size, these tests had very low statistical power; hence the false negative error rate would be high in these analyses.

Table 6 reports the rates of placebo and blinding usage by continent and study type. The only significant finding was that none of the eight pre-operative studies employed blinding, compared to between 33% and 67% of the studies of other types (p=0.019).

4. DISCUSSION

A majority of RCTs presented in this paper score below 18 using the CONSORT statement, producing possible questions regarding validity. There are common omissions related to randomization and blinding technique, sample size calculations and availability of protocols. Similar deficiencies in reporting randomization and blinding were highlighted in the Jadad score.

A combination of these omissions leads us to questioning their reliability. However, when compared to other subject areas, RCTs in skull base surgery score higher than other specialities [11-13]. In addition to this, blinding is difficult to achieve in surgical specialities, especially in relation to surgical technique. As a result, all cases of blinding were in relation to medical treatment or post-operative pain control.

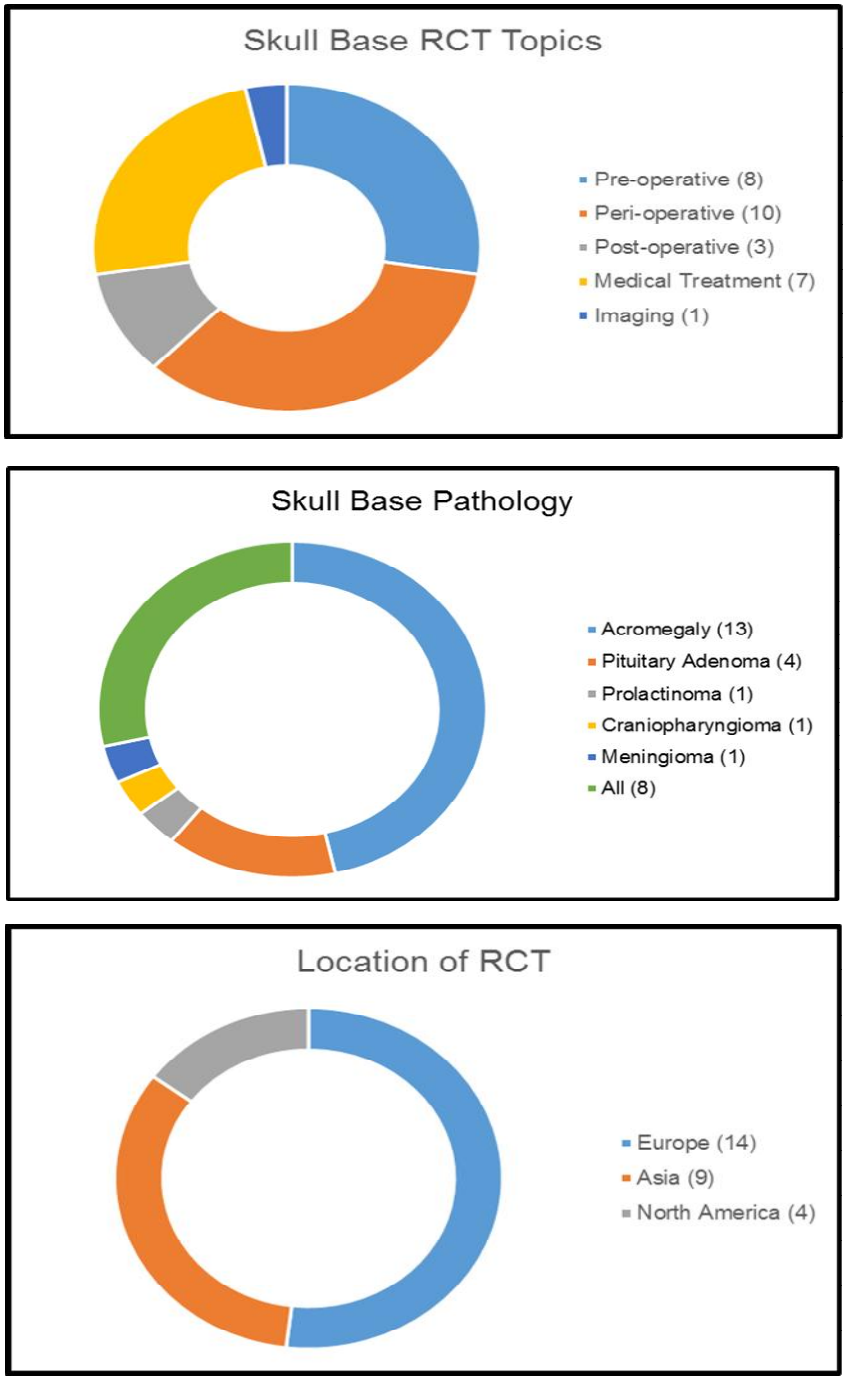

Fig. 2. Distribution of skull base topics, skull base pathology and location of randomised controlled trials

Table 5. Categorical vs. continuous factors

	N	Number of authors	CONSORT (Post-2010)	JADAD	Impact factor (2013)	Year	Patients (N)
Continent		**p=0.002***	**p=0.314**	**p=0.061**	**p=0.003***	**p=0.128**	**p=0.706**
Asia	10	5 (2, 9)	18 (13, 20)	2 (2, 5)	1.75 (0.95, 3.69)	2008 (2001, 2012)	47 (16, 98)
Europe	14	8 (4, 13)	17 (12, 25)	3 (2, 5)	3.35 (2.04, 6.31)	2010 (2001, 2014)	52 (11, 358)
North America	4	5 (3, 7)	20 (17, 21)	5 (3, 5)	2.37 (1.75, 2.37)	2012 (2006, 2013)	80 (20, 130)
Type		**p=0.078**	**p=0.274**	**p=0.149**	**p=0.240**	**p=0.364**	**p=0.154**
Imaging	1	-	-	-	-	-	-
Medical treatment	7	8 (3, 12)	17 (12, 22)	2 (2, 4)	3.35 (1.48, 6.31)	2011 (2001, 2014)	20 (11, 358)
Peri-operative	9	4 (2, 8)	17 (14, 25)	4 (2, 5)	2.36 (0.95, 3.23)	2007 (2001, 2013)	57 (20, 130)
Post-operative	3	7 (5, 8)	20 (17, 21)	3 (2, 5)	2.22 (1.75, 2.37)	2012 (2006, 2012)	68 (40, 120)
Pre-operative	8	8 (4, 13)	19 (14, 21)	3 (2, 3)	3.35 (0.95, 6.31)	2010 (2003, 2014)	55 (16, 98)
Placebo		**p=0.686**	**p=0.021***	**p=0.012***	**p=0.964**	**p=0.135**	**p=0.632**
No	25	7 (2, 13)	17 (12, 22)	3 (2, 5)	2.37 (0.95, 6.31)	2010 (2001, 2014)	44 (16, 358)
Yes	3	5 (4, 8)	21 (19, 25)	5 (4, 5)	3.23 (1.75, 3.35)	2005 (2003, 2006)	90 (11, 120)
Blinding		**p=0.090**	**p=0.127**	**p<0.001***	**p=0.848**	**p=0.601**	**p=0.384**
No	17	8 (2, 13)	17 (12, 21)	2 (2, 3)	2.37 (0.95, 6.31)	2010 (2001, 2014)	44 (16, 98)
Yes	11	5 (3, 12)	19 (13, 25)	4 (2, 5)	2.37 (1.48, 6.31)	2007 (2001, 2014)	57 (11, 358)

*Data reported as median and range, with p-values from Mann-Whitney or Kruskal-Wallis tests, as applicable. *Significant at p<0.05*

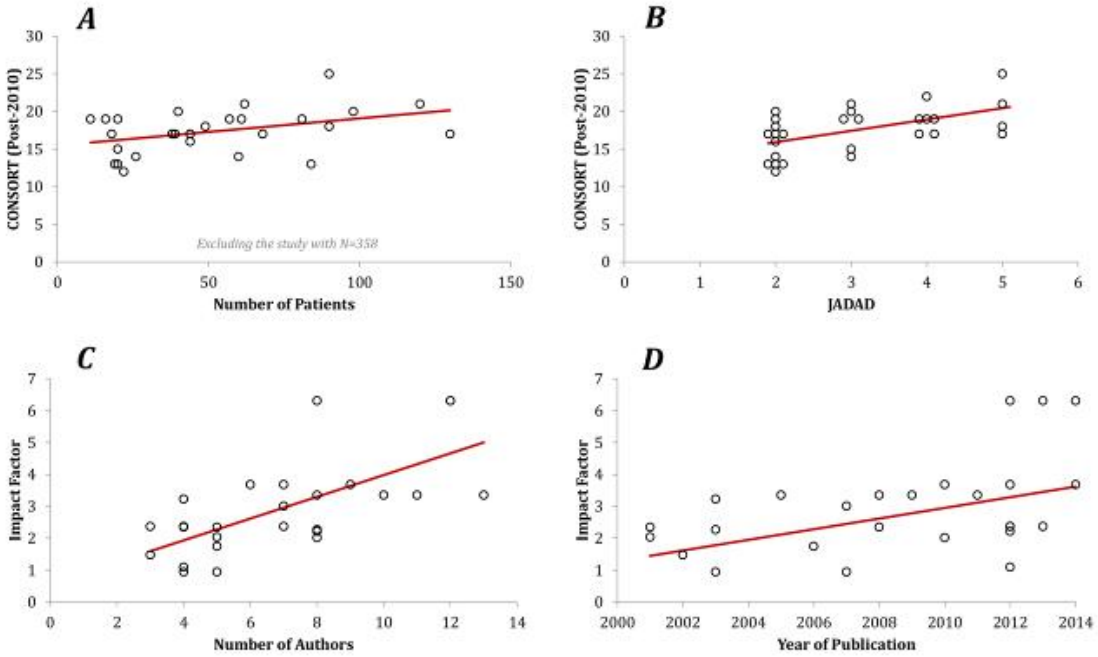

Fig. 3. Regression models

Table 6. Categorical factors

	N	Placebo	Blinding
Continent		**p=0.359**	**p=0.416**
Asia	10	0 (0%)	3 (30%)
Europe	14	2 (14%)	5 (36%)
North America	4	1 (25%)	3 (75%)
Type		**p=0.416**	**p=0.019***
Imaging	1	-	-
Medical Treatment	7	1 (14%)	4 (57%)
Peri-Operative	9	1 (11%)	6 (67%)
Post-Operative	3	1 (33%)	1 (33%)
Pre-Operative	8	0 (0%)	0 (0%)

*P-values from fisher's exact test; *Significant at p<0.05*

Our results suggest that greater number of authors lead to publication within higher impact factor journals, which correlates to a modern initiative of collaborative research. Higher numbers of authors were present in papers from Europe, which significantly differed from other continents worldwide. It was also found that higher CONSORT score were found in papers with larger sample sizes. This was the only variable, in addition to Jadad score, which significantly influenced CONSORT score.

It is interesting to note that the deficiencies of surgical trials to adhere to the CONSORT statement was noted, with revisions made in 2008, creating a CONSORT statement for non-pharmacological treatment [44]. However, it was found that adherence to this revision was even poorer than the original CONSORT statement [45]. In addition to this, the difficulty of utilizing this revision, comparing it to the standard pre-2008 CONSORT statement would make for difficult result analysis. Ultimately it was decided to use the standard CONSORT statements for analysis of RCTs within this study period.

4.1 Limitations

The limitations in this study relate to the fact that analyses are performed are low on power due to the small sample size despite the use of a fourteen year data capture period. Papers prior

to this would not be applicable to modern day management. Unfortunately, we cannot conclude that there is no difference within the non-significant tests, only that the sample size produced did not allow us to encounter one. A large genuine effect could be present within these areas, but would require a larger sample size.

5. CONCLUSION

The CONSORT statement was produced to reduce ambiguity regarding design and reporting of RCTs, with empirical results highlighting correlation with bias. It also has known reliability and external validity. In relation to skull base surgery, a relatively new field within medicine, there are deficiencies in reporting of randomization and blinding technique, sample size calculations and protocol availability. Despite this, there was appropriate reporting of multiple aspects of results and discussion. Our recommendation would be during the conception of RCT protocols, to consider the CONSORT statement, addressing all points with a view of providing easily reproducible results and improvement in readers understanding. This will produced less ambiguous study reporting. We would also respond favourably to a reproduction of our work in future years when greater numbers of studies are available.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Appendix 1. Full list of 73 papers considered

Authors	Paper title	Year of publication
Fougner et al.	Preoperative octreotide treatment of acromegaly: long-term results of a randomised controlled trial.	2014
Colao et al.	Pasireotide versus octreotide in acromegaly: a head-to-head superiority study.	2013
Dixon et al.	Augmented real-time navigation with critical structure proximity alerts for endoscopic skull base surgery.	2013
Casar-Borota et al.	Expression of SSTR2a, but not of SSTRs 1, 3, or 5 in somatotroph adenomas assessed by monoclonal antibodies was reduced by octreotide and correlated with the acute and long-term effects of octreotide.	2013
Olarescu et al..	Inflammatory adipokines contribute to insulin resistance in active acromegaly and respond differently to different treatment modalities.	2013
Yamamoto et al.	Tumor consistency of pituitary macroadenomas: Predictive analysis on the basis of imaging features with contrast-enhanced 3D FIESTA at 3T.	2014
Weissman et al.	Controlled ovarian stimulation using a long gonadotropin-releasing hormone antagonist protocol: a proof of concept and feasibility study.	2013
Marwali et al.	Oral triiodothyronine normalizes triiodothyronine levels after surgery for pediatric congenital heart disease	2013
Baddour et al.	Comparing use of the Sonopet(®) ultrasonic bone aspirator to traditional instrumentation during the endoscopic transsphenoidal approach in pituitary tumor resection.	2013
Farag et al.	Single-blind randomized controlled trial of surfactant vs hypertonic saline irrigation following endoscopic endonasal surgery.	2013
Benson et al.	Effects of standard glucocorticoid replacement therapies on subjective well-being: a randomized, double-blind, crossover study in patients with secondary adrenal insufficiency.	2012
Tam et al.	Olfactory outcomes following endoscopic pituitary surgery with or without septal flap reconstruction: a randomized controlled trial.	2013
Li et al.	Preoperative lanreotide treatment improves outcome in patients with acromegaly resulting from invasive pituitary macroadenoma.	2012
Madsen et al.	Fat content in liver and skeletal muscle changes in a reciprocal manner in patients with acromegaly during combination therapy with a somatostatin analog and a GH receptor antagonist: a randomized clinical trial.	2012
De Capraris et al.	Micro opioid receptor A118G polymorphism and post-operative pain: opioids' effects on heterozygous patients.	2011
Brummelman et al.	Cognitive performance after postoperative pituitary radiotherapy: a dosimetric study of the hippocampus and the prefrontal cortex.	2012
Nizamoğlu et al.	Effects of epidural-and-general anesthesia combined versus general anesthesia during laparoscopic adrenalectomy.	2011
Tutuncu et al.	Comparison of octreotide LAR and lanreotide autogel as post-operative medical treatment in acromegaly.	2012
Morel et al.	Haemodynamic consequences of etomidate administration in elective cardiac surgery: a randomized double-blinded study.	2011
Shah et al.	A controlled laboratory and clinical evaluation of a three-dimensional endoscope for endonasal sinus and skull base	2011

Authors	Paper title	Year of publication
	surgery.	
Engmann et al.	In vitro viability and secretory capacity of human luteinized granulosa cells after gonadotropin-releasing hormone agonist trigger of oocyte maturation.	2011
Karaca et al.	Comparison of primary octreotide-lar and surgical treatment in newly diagnosed patients with acromegaly.	2011
Carlsen et al.	Six-month preoperative octreotide treatment in unselected, de novo patients with acromegaly: effect on biochemistry, tumour volume, and postoperative cure.	2011
D'Haens et al.	Clinical trial: Preliminary efficacy and safety study of a new Budesonide-MMX® 9 mg extended-release tablets in patients with active left-sided ulcerative colitis.	2010
Shen et al.	Effect of presurgical long-acting octreotide treatment in acromegaly patients with invasive pituitary macroadenomas: a prospective randomized study.	2010
Nikoghosyan et al.	Randomised trial of proton vs. carbon ion radiation therapy in patients with chordoma of the skull base, clinical phase III study HIT-1-Study.	2010
Florio et al.	The use of nomegestrol acetate in rapid preparation of endometrium before operative hysteroscopy in pre-menopausal women.	2010
Petersenn et al.	Pasireotide (SOM230) demonstrates efficacy and safety in patients with acromegaly: a randomized, multicenter, phase II trial.	2010
Mao et al.	Preoperative lanreotide treatment in acromegalic patients with macroadenomas increases short-term postoperative cure rates: a prospective, randomised trial.	2010
Matorras et al.	Mid-follicular LH supplementation in women aged 35-39 years undergoing ICSI cycles: a randomized controlled study.	2009
Yang et al.	Clinical evaluation and follow-up outcome of presurgical plan by Dextroscope: a prospective controlled study in patients with skull base tumors.	2009
Younis et al.	Early and short follicular gonadotropin-releasing hormone antagonist supplementation improves the meiotic status and competence of retrieved oocytes in in vitro fertilization-embryo transfer cycles.	2010
Liang et al.	Central nervous system infection in patients with postirradiated nasopharyngeal carcinoma: a case-controlled study.	2009
Sachanandani et al.	The effect of nasally administered budesonide respules on adrenal cortex function in patients with chronic rhinosinusitis.	2009
Toniato et al.	Surgical versus conservative management for subclinical Cushing syndrome in adrenal incidentalomas: a prospective randomized study.	2009
Colao et al.	Octreotide LAR vs. surgery in newly diagnosed patients with acromegaly: a randomized, open-label, multicentre study.	2009
Ali et al.	Bispectral index-guided administration of anesthesia for transsphenoidal resection of pituitary tumors: a comparison of 3 anesthetic techniques.	2009
Fábregues et al.	Transdermal testosterone may improve ovarian response to gonadotrophins in low-responder IVF patients: a randomized, clinical trial.	2009
Carlsen et al.	Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized	2008

Authors	Paper title	Year of publication
	trial.	
Lezoche et al.	Flank approach versus anterior sub-mesocolic access in left laparoscopic adrenalectomy: a prospective randomized study.	2008
Conrad et al.	Overture for growth hormone: requiem for interleukin-6?	2007
Panda et al.	Combination antifungal therapy for invasive aspergillosis: can it replace high-risk surgery at the skull base?	2008
Jain et al.	Excision of pituitary adenomas: randomized comparison of surgical modalities.	2007
Maini et al.	Endoscopic endonasal laser versus endonasal surgical dacryocystorhinostomy for epiphora due to nasolacrimal duct obstruction: prospective, randomised, controlled trial.	2007
Cafiero et al.	Clinical comparison of remifentanil-sevoflurane vs. remifentanil-propofol for endoscopic endonasal transphenoidal surgery.	2007
van Wezel et al.	Differential effects of a perioperative hyperinsulinemic normoglycemic clamp on the neurohumoral stress response during coronary artery surgery.	2006
Jellish et al.	Morphine/ondansetron PCA for postoperative pain, nausea, and vomiting after skull base surgery.	2006
Spies et al.	Intervention at the level of the neuroendocrine-immune axis and postoperative pneumonia rate in long-term alcoholics.	2006
Kim et al.	Differences in the leukocyte response to incision during upper abdominal surgery with epidural versus general anesthesia.	2006
Mishra et al.	The effect of atorvastatin on serum lipoproteins in acromegaly.	2005
Widmer et al.	Cortisol response in relation to the severity of stress and illness.	2005
Gionchetti	Topical treatment of distal active ulcerative colitis with beclomethasone dipropionate or mesalamine: a single-blind randomized controlled trial.	2005
Unfer et al.	Phytoestrogens may improve the pregnancy rate in in vitro fertilization-embryo transfer cycles: a prospective, controlled, randomized trial.	2004
Albu et al.	Small and large middle meatus antrostomies in the treatment of chronic maxillary sinusitis.	2004
Cannavò et al.	Baseline and CRH-stimulated ACTH and cortisol levels after administration of the peroxisome proliferator-activated receptor-gamma ligand, rosiglitazone, in Cushing's disease.	2004
Wong et al.	An open and randomized study comparing the efficacy of standard danazol and modified triptorelin regimens for postoperative disease management of moderate to severe endometriosis.	2004
Westergaard et al.	Placental protein 14 concentrations in circulation related to hormonal parameters and reproductive outcome in women undergoing IVF/ICSI.	2004
Rajaratnam	Hydrocortisone dose and postoperative diabetes insipidus in patients undergoing transsphenoidal pituitary surgery: a prospective randomized controlled study.	2003
Dickey et al.	Highly purified human-derived follicle-stimulating hormone (Bravelle) has equivalent efficacy to follitropin-beta (Follistim) in infertile women undergoing in vitro fertilization.	2003
Palmer et al.	The efficacy and safety of aprotinin for hemostasis during intracranial surgery.	2003
Gargiulo et al.	Remifentanil for intraoperative analgesia during the endoscopic surgical treatment of pituitary lesions.	2003

Authors	Paper title	Year of publication
Jiang et al.	Preliminary exploration of the clinical effect of bleomycin on craniopharyngiomas.	2002
Cho et al.	Comparison of endonasal endoscopic surgery and sublabial microsurgery for prolactinomas.	2002
Lisi et al.	Use of recombinant LH in a group of unselected IVF patients.	2002
Durand et al.	On the mechanisms of action of short-term levonorgestrel administration in emergency contraception.	2001
Cannavò et al.	Effectiveness of slow-release lanreotide in previously operated and untreated patients with GH-secreting pituitary macroadenoma.	2001
Korula et al.	Effect of controlled hypercapnia on cerebrospinal fluid pressure and operating conditions during transsphenoidal operations for pituitary macroadenoma.	2001
European Recombinant LH Study Group.	Human recombinant luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: results of a multicenter double-blind study.	2001
Cordido et al.	Effect of acute pharmacological modulation of plasma free fatty acids on GH secretion in acromegalic patients.	2001
Reynolds et al.	Elevated plasma cortisol in glucose-intolerant men: differences in responses to glucose and habituation to venepuncture.	2001
Watanabe et al.	Suppression of surgical hyperaldosteronism by potassium canrenoate during gynecologic surgery under sevoflurane anesthesia.	2000
Puder et al.	Stimulatory effects of stress on gonadotropin secretion in estrogen-treated women.	2000
Tsagarakis S et al.	The application of a combined stimulation with CRH and desmopressin during bilateral inferior petrosal sinus sampling in patients with Cushing's syndrome.	2000

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