Protocol for a systematic review on classification, outcomes and follow-up of patients undergoing reconstructive surgery after Noma disease-

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Protocol

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Abstract

Background: NOMA is a significant yet neglected disease which affects children in some of the least developed countries in the world. Surgical reconstructive missions for patients affected by NOMA are undertaken regularly by surgeons from more developed countries. However, the long-term benefit and safety of these missions have recently been criticized due to a perceived lack of measurable outcomes and appropriate follow-up. We are conducting a systematic review to critically evaluate the classification systems, outcome measurement tools, and follow-up periods reported in the literature for NOMA disease.

Methods: This systematic review is undertaken following the Preferred Reporting Items for Systematic Reviews and Meta-analyses ("PRISMA") guidelines. The databases MEDLINE, Embase and Web of Science are searched from infinity to 24th of April 2019. All original publications of studies undertaken on reconstructive surgery for NOMA disease, reporting data on outcome after surgery, follow-up time and complications are eligible for inclusion. The primary outcome of interest are the outcome measurement methods used for assessing successful reconstructive surgery after NOMA disease. Other outcomes we are assessing are methods for classification of disease severity and time to last follow-up. The quality of evidence for each summary outcome measure is assessed using the MINORS criteria.

Discussion: Given the precarious situations in the countries where mission surgeons often undertake reconstructive surgery, time pressure and the lack of infrastructure on site prevent them from being able to measure the effect of their surgical outcomes. Our goal is to express the key points of debate and make recommendations for how future surgical missions can be improved. We aim to do so by comparing the current best standards of practice. Publishing this protocol will help future NOMA surgeons plan their missions in a standardised and reproducible way, striving towards a future of worldwide high-quality research.

Systematic review registrations: This protocol was submitted to PROSPERO on the 02.10.2020 and is currently under assessment. (ID 181931)

1 Background

NOMA is a gangrenous ulcerating bacterial disease of multifactorial origin, mostly prevalent in sub-saharan Africa. Due to the high reported mortality rate of up to 85-90%, and the frequent occurrence in extreme poverty regions, WHO has declared NOMA a public health problem in 1994. (1) Global incidence is reported as 30 000-140 000 new cases per year (1, 2), and there are currently 210 000 NOMA survivors worldwide, according to latest estimations (2).

Most cases of NOMA occur between the age of 2-7 years. Malnutrition, poor oral hygiene and poverty are known etiological factors leading to nutritionally acquired immune deficiency syndrome. (3, 4) Children with this syndrome present with lymphatic atrophy and malfunction of cellular immune response, accompanied by an increased vulnerability to infections (5). These preconditions lead to the uptake of pathogens through the gingival mucosa. (6, 7) After uptake of opportunistic pathogens, progression to NOMA disease occurs in several stages, starting with a simple gingivitis and ending in a stage of sequelae including trismus, feeding difficulties and mild to severe disfigurement. (1)

Once the gangrenous gingivitis phase starts, this disease does not confine itself to anatomical or tissue borders. It can destroy the oral mucous integrity, facial fat and soft tissue and invades into the bone of the maxilla and mandible, leading to severe functional deficits (8).

Without appropriate treatment, the majority of affected patients do not survive. They die due to sepsis, aggravation of malnutritional status and following dehydration. Many children die without ever receiving treatment or even diagnosis, due to lack of health care infrastructure, little knowledge and neglect of the disease by the parents.(2)

Purpose of this systematic review is to explore the surgical treatment strategies, patient follow-up and outcomes of surgery with emphasis on outcomes of NOMA surgery.

We are examining the following questions:

1. What are the baseline characteristics of patients undergoing reconstructive surgery for NOMA disease?
2. Which surgical procedures are undertaken to reconstruct the face after NOMA disease?
3. What are the methods/tools for measurement of outcomes for these surgical procedures?
4. Are the current procedures undertaken safe and beneficial for NOMA patients?
 - a. Safety is measured in amount and types of complications and follow-up length
 - b. Benefit is measured as stability of postoperative outcome at follow-up

The main outcomes we are looking at are:

1. Safety and benefit of reconstructive surgery after NOMA disease including number and types of complications and means of measurement of outcome benefit.
2. Long-term benefit of reconstructive surgery after NOMA disease in the long-term follow-up including means of measurement of outcome benefit.

Other outcomes of interest are:

3. Overview on the basic characteristics of the studies including number of patients that received surgery, gender, health status prior to surgery (weight, BMI, comorbidities)

- Overview on the disease characteristics of the patients including affected areas and functions of the face and the classification of these
- Overview on type of surgical intervention received, including site of intervention, type of surgeon (local or mission surgeon), number of operations needed and hospital duration

2 Methods

A comprehensive, structured literature search of published articles is conducted. This is designed by the author S.S and performed in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), the standardized PRISMA-P checklist can be found in the supplementary material (9).

2.1 Data sources

The literature search is performed using the electronic databases MEDLINE (PubMed), EMBASE and Web of Science. The keywords used in the search are selected from key papers and are described in tables below. Search strings 1 and 2 are combined using the Boolean term AND, then the limits are applied. Furthermore, a ‘MeSH term’ search is conducted, and the reference lists of included articles are reviewed for any additional articles.

Search strategy for Embase.com (15.04.2020)

/exp = EMtree keyword with explosion
.tw = The Textword field in EMBASE includes Title (TI) and Abstract (AB).

Table 1- Search Strategy used in EMBASE

Number	Search terms	Results
#1	exp plastic surgery/ OR exp surgeon/ OR exp plastic surgeon/ OR exp esthetic surgery/ OR exp skin transplantation/ OR exp microsurgery/ OR exp tissue flap/ OR exp Z plasty/ OR exp surgical flaps/ OR exp reconstructive surgery/ OR exp face surgery/ OR exp maxillofacial surgery/ OR exp oral surgery/ OR skin graft*.tw. OR full thickness graft*.tw. OR SSG.tw. or FTG.tw OR axial flap*.tw. OR pedicled flap*.tw. OR surgical flap*.tw. OR contracture release*.tw. OR exp free tissue graft/ OR free flap*.tw. OR regional flap*.tw. OR exp skin flap/ OR local flap*.tw. OR surger*.tw. OR surgical*.tw. OR operation*.tw. OR operative*.tw. OR incisi*.tw. OR excisi*.tw. OR management*.tw. OR treatment.tw	8557452
#2	Exp Vincent stomatitis/ OR acute necrotizing ulcerative gingivitis.tw OR acute necrotising ulcerative gingivitis.tw OR acute ulcerative gintivitis.tw OR noma.tw OR cancrum oris.tw	1401
#3	#1 AND #2	639
Limits: Publication prior to final search, April 15th, 2020		

Source: Authors table

Search strategy for MEDLINE (PubMed) (15.04.2020)

/exp = MEDLINE keyword with explosion/ Mesh terms
.tw = The Textword field in MEDLINE includes Title (TI) and Abstract (AB).

Table 2- Search Strategy used in MEDLINE

Number	Search terms	Results
#1	exp Reconstructive Surgical Procedures/ OR exp Surgery, Plastic/ OR exp Tissue Transplantation/ OR exp Surgical Flaps/ OR exp Skin Transplantation/ ORexp Free Tissue Flaps/ OR exp Microsurgery/ OR exp Surgery, Oral/ OR exp Surgical Procedures, Operative/ OR exp "Oral and Maxillofacial Surgeons"/ OR exp Surgeons/ OR skin graft*.tw. OR full thickness graft*.tw. OR SSG.tw. OR FTG.tw. OR axial flap*.tw. OR pedicle flap*.tw. OR pedicled flap*.tw. OR surgical flap*.tw. OR contracture release*.tw. OR free flap*.tw. OR regional flap*.tw. OR local flap*.tw. OR surger*.tw. OR surgical*.tw. OR operation*.tw. OR operative*.tw. OR incisi*.tw. OR excisi*.tw. OR management*.tw. OR treatment*.tw	8167413
#2	exp Noma/ OR cancrum oris.tw. OR exp Gingivitis, Necrotizing Ulcerative/ OR acute necrotizing ulcerative gingivitis.tw. OR acute necrotising ulcerative gingivitis.tw.	1664
#3	#1 AND #2	568
Limits: Publication prior to final search, April 15th, 2020		

Source: Authors table

Search strategy for Clarivate Analytics/Web of Science (15.04.2020)

TOPIC = words in title, abstract or keywords
ndexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Table 3- Search Strategy used in Web of Science

Number	Search terms	Results
#1	TS= (surger* OR surgical* OR surgeon* OR operation* OR operative* OR incisi* OR extracti* OR excisi* OR management* OR treatment*)	9,621,445
#2	TS= (reconstructi* OR cosmetic* OR esthetic* OR aesthetic* OR plastic OR corrective* OR oral* or *maxillofacial* OR facial OR face* OR "head and neck" OR flap* OR skin* or micro*)	8,095,337
#3	TS= (noma OR "cancrum oris" OR "necrotizing ulcerative gingivitis" OR "acute necrotizing ulcerative gingivitis" OR "acute necrotising ulcerative gingivitis")	3,515
#4	#2 AND #1	1,821,209
#5	#4 AND #3	186
Limits: Publication prior to final search, April 15th, 2020		

The PRISMA flow chart is used to display the selection and inclusion/exclusion of articles in the screening process, as seen below.

Source: Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4:1.

2.2 Study eligibility criteria

Articles are eligible for inclusion if they provide primary empirical evidence of patient outcomes after NOMA surgery. The full inclusion and exclusion criteria are detailed in the table below. Study selection was independently assessed by 2 reviewers (S.S. and M.B.), any persisting disagreements were reviewed and adjudicated by a third reviewer (H.K.).

Table 5- Inclusion/exclusion criteria for study selection

Inclusion Criteria
1. Original publications
2. Human subjects
3. Case Series, Retrospective Data Analyses, Clinical Trials, Controlled Clinical Trials, Prospective Studies
Exclusion Criteria
1. Publication type does not match inclusion criteria (Review articles, Mixed methodology studies without subgroup data, Animal studies, Conference Articles)
2. Conditions other than NOMA, Cancrum Oris, or Necrotizing Ulcerative Stomatitis not related to NOMA
3. The paper is about conditions located at sites other than the Maxillofacial and Head and Neck region
4. The paper is not about treatment
5. The paper is not about a surgical intervention (but included if terms such as reconstruction or rehabilitation, or flap or graft, are mentioned).
6. The paper is about prevention rather than treatment of NOMA

Source: Authors table

2.3 Data extraction and analysis

Articles are appraised and data extracted using a structured, pro forma designed a priori from the Cochrane Collaboration's data collection form for intervention reviews, see the table below. This data collection template is pilot tested in randomly selected articles, before being used to assess all included articles. Data extracted includes patient demographics (gender, age, comorbidities), the details of the surgical procedure used (technique, surgery time, intraoperative complications) and any outcome measures reported including time to outcome measurement and any complications (see Appendix 1).

2.4 Methodological Quality and Assessment of Bias

Article review includes analysis of study design to ascertain risk of bias. Studies are also assigned a level of evidence based on the Oxford Centre for Evidence Based Medicine (10). Included articles are rated for methodological quality using the MINORS criteria as seen in appendix 2 (11).

Table 6- Adapted form of Oxford Levels of Evidence

Level of Evidence	Types of Studies
I	SR (with homogeneity) of RCTs, Individual RCT (with narrow Confidence Interval),
II	SR (with homogeneity) of cohort studies, Individual cohort study (including low quality RCT; e.g., <80% follow-up), "Outcomes" Research; Ecological studie
III	SR (with homogeneity*) of case-control studies, Individual Case-Control Study
IV	Case-series (and poor quality cohort and case-control studies)
V	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Source: Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plastic and reconstructive surgery*. 2011;128(1):305-10.

2.5 Statistical analysis

Data are analysed using IBM SPSS statistics version 24. Descriptive statistics are performed where possible to permit for narrative synthesis. Meta-analysis is performed for outcomes of interest where at least three comparative studies, with low risk of bias, report the same outcome variable.

Abbreviations

CEBM- Center of evidence-based medicine

IQR- Interquartile range

MINORS- Methodological index for non-randomized studies

MO- Mouth opening

NOITULP- anagram as classification system for NOMA disease

PRISMA- Preferred reporting items for systematic reviews and meta-analyses

WHO- World Health Organization

Declarations

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of supporting data

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BL, SS and WR designed the study in cooperation. SS and HK planned the original review protocol, which was revised by WR. MB and SS conducted the pilot literature searches, SS built and carried out the final search. SS drafted the manuscript with inputs by BL. WR and HK contributed to manuscript revision. All authors read and approved the final manuscript prior to submission. SS is the primary author and guarantor of this protocol.

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Appendix

Study Descriptives						Demographics and Comorbidities								
Study No.	Authors	Year	Country	Study Type	Level of Evidence	No of Patients Included	age	sex	BMI	Smoker	Malnutrition	HIV positive	Measles	Tuberculosis

Surgery						Outcomes					
mean no. of operations	Distracteur implantation	Free microsurgical flap	Regional Flap	Local Flap	Excision and direct closure	follow up time	no. of complications	objective outcomes-short term	subjective outcomes-short term	objective outcomes-long term	subjective outcomes-long term

MINORS Criteria													
Study No.	1	2	3	4	5	6	7	8	9	10	11	12	Total

Criteria: 1: a clearly stated aim, 2: Inclusion of consecutive patients, 3: prospective collection of data, 4: endpoints appropriate to the aim of the study, 5: Unbiased assessment of the study endpoint, 6: Follow-up period appropriate to the aim of the study, 7: Loss to follow-up less than 5%, 8: Prospective calculation of the study size, 9: An adequate control group, 10: Contemporary groups, 11: Baseline equivalence of groups, and 12: Adequate statistic analyses. The items are scored 0 (not reported or inadequate) or 1 (adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies

Appendix 2- MINORS CRITERIA

Table 7- MINORS Criteria

MINORS criteria
1. A clearly stated aim: the question addressed should be precise and relevant in the light of available literature
2. Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)
3. Prospective collection of data: data were collected according to a protocol established before the beginning of the study
4. Endpoints appropriate to the aim of the study: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.
5. Unbiased assessment of the study endpoint: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated
6. Follow-up period appropriate to the aim of the study: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events
7. Loss to follow up less than 5%: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint
8. Prospective calculation of the study size: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes
Additional criteria in the case of comparative study
9. An adequate control group: having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data
10. Contemporary groups: control and studied group should be managed during the same time period (no historical comparison)
11. Baseline equivalence of groups: the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results
12. Adequate statistical analyses: whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk

Source: Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003;73(9):712-6.

Figures

Figure 1

Table 4- PRISMA flow chart for article selection process. Source: Moher D, Shamseer L, Clarke M, Gherzi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMAPchecklistNOMA.docx](#)