Non-physician Out-of-hospital Rapid Sequence Intubation Success and Adverse Events: a Systematic Review and Meta-analysis

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Author contributions

PF conceived of the study, JC and PF completed the literature search, PS and PF did the data extraction. CS and PF completed the quality ratings, and SD and PF analysed the data. All contributed to the manuscript. PF takes responsibility for the paper as a whole.

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Abstract

Introduction

Rapid sequence intubation (RSI) performed by non-physicians such as paramedics or nurses has become increasingly common in many countries, however concerns have been stated regarding the safe use and appropriateness of RSI when performed by these healthcare providers. The aim of our study was to compare RSI success and adverse events between non-physician and physician in the prehospital setting.

Methods

A systematic literature search of key databases including Medline, EMBASE, and the Cochrane Library was conducted. Eligibility, data extraction and assessment of risk of bias were assessed independently by two reviewers. A bias-adjusted meta-analysis using a quality effects (QE) model was conducted for the primary outcomes of overall ETI success and first pass ETI success and for adverse events where possible to do so.

Results

Eighty-three studies were included in the meta-analysis. There was a 2% difference in successful ETI proportion for physicians versus non-physicians; 99% (95% CI 98-99) versus 97% (95% CI 95-99). A 10% difference in first pass RSI success was noted between physicians 88% (95% CI 83-93) versus 78% (95% CI 65-89) for non-physicians. For airway trauma, bradycardia, cardiac arrest, endobronchial intubation, hyper and hypotension lower adverse events were noted for physicians. However, non-physicians had a lower prevalence of hypoxia and oesophageal intubations. Similar proportions were noted for pulmonary aspiration and emesis. Nine adverse events estimates lacked precision except for endobronchial intubation and four adverse event analyses showed evidence of possible publication bias. Consequently, no reliable evidence exists for differences between physicians and non-physicians for adverse events.

Conclusion

This analysis shows that physicians have a higher RSI first pass and overall success as well as mostly lower adverse events for RSI in the out-of-hospital setting. Nevertheless, for all success and adverse events no firm conclusion for a

difference can be drawn due to lack of precision of meta-analytic estimates or selective reporting. First pass success could be an area in which to focus quality improvement strategies for non-physicians.

Introduction

Rapid sequence intubation (RSI) is an advanced airway management process whereby rapidly acting sedative and paralytic drugs are used to aid the placement of an endotracheal tube. The practice of RSI is intended to optimally prepare patients for laryngoscopy and endotracheal intubation (ETI) and to facilitate conditions for successful intubation on the first attempt. Prehospital RSI is utilized by a number of emergency medical services (EMS) in regions such as Australia,[1] Europe,[2] South-Africa[3], and the United States[4]. Previous work involving paramedics in the United States suggested the prehospital RSI may increase mortality in patients with traumatic brain injury.[5] Davis et al theorized this difference may be related to the low paramedic intubation success rate (84%), multiple, severe hypoxic episodes and frequent hyperventilation, suggesting safety concerns surrounding RSI by non-physicians.[5,6] A meta-analysis by Lossius et al found lower success rates for intubation after RSI by non-physicians when compared to physicians (99 versus 96%) and suggested that the prehospital use of intubation should be reconsidered in the absence of a physician.[2]

Other research has also raised concerns regarding non-physician RSI and intubation in the prehospital setting.[7-16] Dunford reported that 57% of their cohort had desaturation events after paramedic RSI, and 48% had recognised oesophageal intubations.[17] A South-African paramedic RSI program reported a success rate of 100%, but the authors also reported adverse events of up to 22% and raised concerns about the safety of this RSI program.[3] In a meta-analysis of the effect of clinician experience on mortality after endotracheal intubation there was a twofold increase in the odds of mortality when inexperienced (primarily paramedics) intubate.[18] Peters et al compared intubation of paramedics in helicopter EMS to physicians, and found first-pass success rate lower when ambulance paramedics were compared with physicians (46.4 vs. 84.5%).[19] However, there is some evidence that the success and adverse event profile for non-physician RSI might not be as poor as these studies suggest. A randomized controlled (RCT) trial by Bernard et al from Australia found favourable neurological outcome at six months after paramedic RSI compared to in-hospital RSI.[1] In contrast to the Davis trial, hyperventilation and hypoxia were uncommon and intubation success rate considerably higher (97.5%).[1] The Bernard trial suggests that for some non-physicians RSI might not be as unsafe as previously suggested and highlights the need for further investigation. Against that background, the

aim of this study was to conduct a systematic review that compares RSI success and adverse events between non-physician and physician in the prehospital setting by analysing success and adverse events.

Methods

This systematic review and meta-analysis was conducted according to the PRISMA guidelines, [20] and was registered with the PROSPERO registry of systematic reviews (registration number 42014014834).

Data Sources, Search Strategy and Study Selection

Medline, EMBASE, and the Cochrane Central Register of Controlled Trials were searched by two authors independently (JC and PF) from the inception of each database up to February 11, 2016 (search terms in Appendix 1). This was complemented by back-searching the reference lists of identified studies for suitable articles. Abstracts of potentially suitable articles were screened by two authors (JC and PF) for relevance. Full text articles were screened by the same authors.

Eligibility Criteria

All out-of-hospital English language observational and experimental studies that reported RSI success proportions or harms by out-of-hospital personnel (all healthcare workers able to perform RSI) were eligible. Observational studies were defined as etiologic or effectiveness studies using data from databases that includes prospective and retrospective cohorts, case control, cross sectional, case series and studies using historical controls[21]. RSI drugs include the use of a paralytic agent, such as suxamethonium (succinylcholine), rocuronium and vecuronium. The time frame for the selected studies was not limited. Publication types in which such studies were sourced from included journals, books, dissertations, technical reports and manuscripts. We excluded manikin and animal studies; those examining other advanced airways such as supraglottic airways; studies that reported non-drug assisted ETI results or that report ETI results assisted with drugs other than typical RSI drugs, for example ETI assisted with benzodiazepines only. We further excluded those that appeared in abstract only; that reported results from which it was not possible to extract effect size statistics; and where it was impossible to assess the methodological quality of the paper.

Data Abstraction

Two authors (PS and PF) independently reviewed each included study to identify the following characteristics: study and year; country; paralytic drug; clinician intubating after RSI drugs were administered; type of emergency medical service (ground or flight); overall success proportion; first pass success; oesophageal intubation; cardiac arrest during or after RSI; hyper- or hypotension during or after RSI; hypoxia or desaturation events during or after RSI; emesis during or after RSI; brady- or tachycardia during or after RSI; endobronchial intubations; hypo- or hypercarbia during or after RSI; aspiration during or after RSI; pneumonia and airway trauma. We extracted estimates only if it was clear from the manuscript that an event happened during or after the RSI procedure. Extraction was piloted for clarity on five studies. Disagreements in extracted data were resolved by arbitration and consensus by all authors.

Quality Assessment

We assessed the quality (extent of bias) of each study with a checklist adapted from the prevalence checklist of Hoy et al (Appendix 2).[22] To aid quality ratings, we designed a guide that accompanied the checklist (Appendix 3). Modifications included paraphrasing the wording of each item in the Hoy checklist for the RSI and out-of-hospital checklist. The checklist consisted of eight items that assessed external and internal validity via four domains: selection and nonresponse bias, measurement bias and bias related to the analysis.[22] Two authors (CS and PF) independently assessed all included studies for quality, and interrater agreement was assessed with an intraclass correlation coefficient (ICC).[23,24]

Definitions

We used success and adverse event definitions provided by the authors of the included studies. The adequacy of a particular study definition was formally assessed through the quality rating, and specific standards for definitions are presented in the guidelines for the quality checklist in item six (Appendix 3). Physicians were defined as clinicians that had undergone training to qualify them as medical doctors and included anaesthesiologists and emergency physicians. Non-physicians were defined by exclusion: clinicians able to perform RSI that were not physicians and included paramedics, nurses, firefighter/paramedics, respiratory therapists and physician assistants.

Statistical Analysis

The main outcomes were the proportions (expressed as a percentage) of 1) overall success of intubation after RSI drugs; 2) first pass success; and 3) the various adverse events. When proportions approach 1 (such as with intubation success) the typical equation for a confidence interval does not prevent confidence intervals falling outside the range of 0 – 1.[25] Furthermore, when the proportions are very small or large, the variance is pressed towards zero and meta-analysis puts undue weight on studies with extreme proportions.[25] To avoid this pressing effect of the variance and the confidence interval outside the possible range, the double arcsine square root transformed prevalence proportion across studies was pooled and results were reported after back-transformation to natural proportions. While the usual transformation is the logit transformation, the double arcsine square root has been shown to be better at variance stabilization.[25]

Meta-analyses were conducted for outcomes that had similar definitions and were therefore considered conceptually a single group. If multiple studies reported data on the same subjects (i.e. from the same dataset), we selected the least biased study based on the quality assessment to avoid counting data twice. Heterogeneity was determined to be present when the value of τ^2 was greater than zero. Both are presented because at higher levels of heterogeneity, for similar I^2 the Cochran's Q can still vary considerably. Meta-analyses of heterogeneous studies is often performed using the random effects (RE)model, [26] however our analysis was completed using the quality effects (QE) model described by Doi et al.[27,28] The QE model adjusts for study-level risk of bias and has advantages over the RE model, given that the RE model estimate does not allow for direct interpretation.[29] Also, the RE estimator suffers from faulty error estimation so that confidence intervals generated are too narrow,[30] and the RE model also exacerbates estimation of publication bias.[31] Study level-risk of bias was quantified for use in the QE model by averaging the summary quality ratings of each rater. (Table 1)

Funnel plots were not used because they perform poorly when the effect size is a prevalence proportion such as in this analysis,[32] for this reason publication bias was examined visually by Doi plots and the Luis Furuya-Kanamori (LFK) index.[24,33] The Doi plot uses linear ranking to study asymmetry, where a symmetrical triangle is created with a z-score close to zero at its peak if the studies in the analysis are homogenous and not affected by selection or other forms of bias.[24] The LFK index indicates no asymmetry if within ±1, minor asymmetry if more

±1 but within ±2 and major asymmetry if the index exceeds ±2.[33] Pooled estimates between physicians and non-physicians were considered similar if there was an overlap of 95% confidence intervals.

Results

The literature search identified 3351 articles. After abstract screening and duplicate removal, 89 articles were included in the systematic review, with 83 suitable for meta-analysis (Figure 1). A comprehensive listing of the 89 articles undergoing qualitative assessment including a description of the study characteristics, intubation success rates and proportions of adverse effects are shown in Table S1.

Characteristics of the studies

Eleven studies were non-randomized trials,[6,9,34-42] and two were randomized controlled trials.[1,43] Twenty-five were prospective[7,10,11,17,44-64] and 51 were retrospective studies.[3-6,8,12,13,15,16,19,65-105] Physicians were the intubating clinicians in 18% of studies,[8,10,11,15,16,19,35,51,53,58,61,71,76,82,85,97] 28% were a mix of physicians and non-physicians,[4,7,12,36,44,46,48,49,52,54,59,60,62-64,77,78,88,90,91,96,99,101,104,105] and 54% were non-physicians.[1,3,5,6,9,13,17,34,37-43,45,47,50,55-57,65-70,72-75,79-81,83,84,86,87,89,92-95,98,100,102,103,106] About half of studies (47%) were reports from flight medical programs. Four studies in this review were excluded from the meta-analysis to avoid double counting,[3,49,63,72] and two were reviewed without meta-analysis.[6,106] The number of individual RSIs included in the overall success analysis is 26 353, and 11 349 for the analysis of first pass success (Table 1).

Study Quality

Two raters had moderate agreement with ICC (3, k) of 0.52 (95% CI 0.20- 0.74). Study quality was higher for studies that reported physician RSI with a mean of 6.28 (95% CI 5.76 – 5.80) out of a possible eight, compared to non-physicians 5.43 (95% CI 5.20 – 5.63) and physicians/non-physicians 5.20 (95% CI 4.78 – 5.62) (Table 1).

Quantitative Synthesis

Overall and first pass success of endotracheal intubation after rapid sequence induction

Meta-analysis shows a two percent difference in the overall success between physicians and non-physicians; 99% (95% CI 98-99) versus 97% (95% CI 95-99) (Table 1, Figure 2 and Table S3). There was a 10% lesser first pass success for non-physicians compared to physicians; 78% (95% CI 65-89) versus 88% (95% CI 83-93) (Table 1, Figure 2 and Table S4). However, these estimates lacked precision as evidenced by overlapping confidence intervals. The Doi

plots for the overall and first-pass success meta-analyses were symmetrical (not shown) and LFK indices indicate symmetry (Table S2).

Adverse events

Point estimates for non-physicians show 3% less oesophageal intubations and hypoxia, 1% more cardiac arrest, 3.7% more endobronchial intubation, 3.5% more bradycardia, 1% more hypertension, 1% more hypotension, and 1% more airway trauma than physicians (Table 1, Tables S5 to S12, Figure 2). No difference in point estimates was seen for emesis or pulmonary aspiration (Table 1, Table S13 and S14, Figure 2). All estimates except endobronchial intubation lacked precision and therefore the magnitude and direction of the estimates overlapped for most adverse events. Doi plots and LFK indices showed gross positive asymmetry in effect sizes for four adverse events: Esophageal intubation, endobronchial intubation, bradycardia and hypertension (Figure S1 and Table S2). No meta-analysis for tachycardia could be completed as insufficient studies reported purely physician estimates. Furthermore, no meta-analysis for hyperventilation/hypocarbia or pneumonia was completed as insufficient studies or unsuitable estimates reported to make a physicians and no-physicians comparison.

Heterogeneity

All analyses showed large heterogeneity except for pulmonary aspiration. Also, there was larger heterogeneity in the overall success proportions of non-physicians with I^2 = 92% compared to physicians I^2 = 74% (Table 1). High heterogeneity was not only evident for overall success, but a pattern of higher heterogeneity for non-physicians is evident across all analysis where such a comparison was possible.

Limitations

Our systematic review found large heterogeneity across most analysis, similar to other meta-analysis of advanced airway management.[107,108] This large heterogeneity warrants caution in interpreting our estimates. There was evidence for possible publication bias for four adverse events, raising the likelihood of selective reporting and making assessments of these four adverse events unreliable. Comparisons of the estimates from this analysis with nationwide results such as those from the NEMESIS data provide further evidence for possible selective reporting. As such, it is argued that the pooled results from this analysis might not be unbiased. Also, painstaking efforts were made to avoid the “unit of analysis” problem where some subjects are counted twice due to studies reporting the same subjects across multiple papers. Even so, the data from Tollefsen et al might overlap very slightly with the data

from NEMESIS reported by Wang, but a sensitivity analysis shows that excluding Tollefsen does not change the pooled results.[4,100] Only English publications were included in this review, and it is possible that a small number of non-English publications exist. Should that be the case, it is unlikely that such studies will alter these estimates and conclusions.

It would have been ideal to meta- analyse clinician types separately, but lack of sufficient data for some clinician types made such analysis unfeasible. Analytic pooling of all non-physician types probably obscures important differences. Separate analysis could reveal how clinician type causes heterogeneity which would allow for more focused research and training. Finally, the training level of the non-physicians provider (experienced, novice, etc.) was not provided. While experience and level of training impact ETI success, datasets such as NEMSIS do not report provider proficiency with ETI. The interrater agreement beyond chance in this analysis can be considered moderate. A higher agreement would have been ideal, but we believe this moderate agreement does not negate our results. Numerous studies reported adverse events that were unsuitable for meta-analysis. As an example, consider oesophageal intubation reports. Twelve studies that were not included in the esophageal intubations analysis reported these events, but in such a way that they were not useful; e.g. they reported "no *unrecognised* esophageal intubations",[34] which did not reveal the actual number of such mishaps. This proved to be a problem with reports of endobronchial intubations too. A lack of adequate reporting and failure to publish these estimates in these instances could explain the asymmetry in the Doi plots (Figure S1).

Discussion

This systematic review provides an up-to-date synthesis of non-physicians RSI success and adverse events. Our meta-analysis showed a two percent difference in the overall success in favour of physicians; however a lack of precision of this estimate suggests that the evidence for these differences might not be reliable. Additionally, a ten percent difference in the first pass success favours physicians. Furthermore, our results show that for six of the ten adverse events, pooled estimates show lower adverse events for physicians. Nevertheless, for inadvertent oesophageal intubation and hypoxia non-physicians events have more favourable proportions. Large overlap in confidence intervals for nine of the adverse events makes these differences less-than-reliable, except for RSI-related endobronchial intubation which had no overlap. Evidence suggestive of selective reporting/publication for RSI-related bradycardia and hypertension and also for inadvertent endobronchial and oesophageal intubation makes the

estimates of these adverse events less dependable. Additionally, Doi plots showed gross *positive* asymmetry for these four adverse events, which could mean that lower event rates for were under-reported for non-physicians. It follows that none of the differences noted for adverse events could be taken as very trustworthy. In most analyses, larger heterogeneity is present among the estimates of non-physicians, showing that success and adverse events are more variable amongst non-physicians, perhaps due to varying levels of skill or training.

A ten percent difference in first pass success when physicians are compared to non-physicians might be a cause for concern. It is best to intubate on the first attempt, as repeated attempts at intubation and laryngoscopy have been associated with increased adverse events such as hypoxemia, oesophageal intubation, aspiration, cardiac arrest and decreased likelihood of return-of-spontaneous circulation. [109-112] We consider the first pass proportion of out-of-hospital physicians the benchmark; non-physicians should strive to match physician first pass success. A lack of sufficient or suitable studies precluded a comparison of hyperventilation. Even so, Davis et al report a 59% rate of hypocarbia ($EtCO_2 \leq 25$ mmHg) in their paramedic RSI trial,[6] and rates of 9.5% ,[106] as well as 50% (EtCO2 ≤30 mmHg) were found in in other publications .[48] These high hyperventilation rates contrast with the low paramedic hyperventilation proportions from South Africa (2%).[3] A United States ground-based paramedic study reported 10% hyperventilation/hypocarbia. [56] Similarly, we were unable to analyse hypoventilation or hypercarbia due to insufficient studies that report estimates suitable for analysis. Nevertheless, Bernard et al found a 20% instance of hypoventilation for paramedics ($EtCO_2 \geq 45$mmHg), [66] but Gunning et al. found a 1% prevalence in a South African RSI program.[3] In a mixed physicians and non-physicians crew, Holmes et al. report a 7.6% proportion[54] while Sing et al. report no cases of hypoventilation or hypercarbia for their nurse/paramedic crew. [93,94] No analysis for pneumonia were completed for similar reasons, however Davis et al. report 20% pneumonia prevalence in their paramedic based study.[5] Sing et al. demonstrate 17.5% and 21% proportion in the nurse/paramedic configuration. [93,94] For a non-physician/physician crew Sloane et al. report a 30% prevalence of post-RSI pneumonia.[96] Since we could not analyse hypo or hyperventilation, pneumonia and tachycardia, we cannot make a meaningful comparison for these four events between physicians and non-physicians.

We found variations in the definitions used for adverse events for the studies included in this review. For example, the analysis of hypoxia/desaturation revealed at least seven distinct but related definitions, and this could be a likely source of the heterogeneity seen in the analysis of adverse events. Sollid et al devised a template to solve

this lack of uniform reporting by devising standardised definitions for advanced airway management.[112] Future studies should consider reporting their RSI results using the template by Sollid et al. To reduce heterogeneity in adverse events and success estimates, uniform data collection and standardized definitions are critical and make comparison of RSI successes and adverse events easier. Another possible cause of heterogeneity was the extent of bias (study quality) of estimates included in this review. Specifically, studies that report physician success and adverse events are consistently less biased than those from non-physicians, as the quality ratings show. It is strength of the QE method that our results are adjusted for these study level biases.

Conclusions

This analysis shows that physicians have a higher RSI first pass and overall success as well as mostly lower adverse events for rapid sequence intubation in the out-of-hospital setting. Nevertheless, for all success and adverse events no firm conclusion for a difference can be drawn due to lack of precision of meta-analytic estimates or due to possible selective reporting. First pass success could be an area in which to focus quality improvement strategies for non-physicians.

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