Original Article

Prediction of difficult mask ventilation using a systematic assessment of risk factors vs. existing practice – a cluster randomised clinical trial in 94,006 patients

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Summary

We compared implementation of systematic airway assessment with existing practice of airway assessment on prediction of difficult mask ventilation. Twenty-six departments were cluster-randomised to assess eleven risk factors for difficult airway management (intervention) or to continue with their existing airway assessment (control). In both groups, patients predicted as a difficult mask ventilation and/or difficult intubation were registered in the Danish Anaesthesia Database, with a notational summary of airway management. The trial's primary outcome was the respective incidence of unpredicted difficult and easy mask ventilation in the two groups. Among 94,006 patients undergoing mask ventilation, the incidence of unpredicted difficult mask ventilation in the intervention group was 0.91% and 0.88% in the control group; (OR) 0.98 (95% CI 0.66–1.44), p = 0.90. The incidence of patients predicted difficult to mask ventilate, but in fact found to be easy ('falsely predicted difficult') was 0.64% vs. 0.35% (intervention vs. control); OR 1.56 (1.01–2.42), p = 0.045. In the intervention group, 86.3% of all difficult mask ventilations were not predicted, compared with a higher proportion 91.2% in the control group, OR 0.61 (0.41–0.91), p = 0.016. The systematic intervention did not alter the overall incidence of unpredicted difficult mask ventilations, but of the patients who were found to be difficult to mask ventilate, the proportion predicted was higher in the intervention group than in the control group. However, this was at a 'cost' of increasing the number of mask ventilations falsely predicted to be difficult.

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Introduction

Facemask ventilation is an essential component of airway management. Predicting airway management difficulties remains a challenge [1]. Better prediction may reduce morbidity and mortality by adequate allocation of relevant personnel and the use of appropriate equipment [2].

The 4th National Audit Project (NAP4) and major national anaesthesia societies recommend a pre-operative assessment of every patient's airway [1, 3–5]. However, it remains unclear how this airway assessment should be performed and how it might relate to risk of difficult mask ventilation [6]. The incidence of difficult mask ventilation is ~2–6 in 300 [7–10]. Difficult mask ventilation has been shown to be associated with difficult intubation, and the incidence of combined difficult mask ventilation and difficult intubation is ~1 in 300 [9, 11]. Although rarely occurring, the 'cannot intubate – cannot ventilate' situation accounts for > 25% of all anaesthesia-related deaths [1]. However, few studies have investigated risk/predictive factors [7, 8, 10, 11]. Moreover, it has not been established that systematic prediction of difficult mask ventilation is beneficial. Because it is not easy to perform trials on rare, adverse events, the impact of these tools are therefore seldom tested [12], but cluster randomisation offers an effective means of study [13, 14].

We have previously reported the diagnostic accuracy of difficult mask ventilation prediction to be poor, with 94% of all difficult mask ventilations being unpredicted [9]. We hypothesised that by introducing a hospital-wide protocol, we could better predict difficult mask ventilation (and indeed, combined difficult mask ventilation and difficult intubation). Our main aim was to compare the effect of this systematic assessment protocol vs. existing practice (i.e. no fixed protocol).

Methods

The Difficult Airway Management Trial (DIFFICAIR) was a cluster randomised trial in which 28 Danish anaesthesia departments (each expected to recruit > 200 patients whose tracheas were intubated) were randomly allocated (matched 1:1 in equal proportions) to an 'intervention' group using systematic prediction of difficult airway management or a 'control' group that continued existing practice. All patients ≥ 15 years of age who had undergone attempts at mask ventilation were included. The departments were randomly assigned (computer generated) based on the proportion of unpredicted difficult intubations in 2011 (Danish Anaesthesia Database data < 2% or ≥ 2%). All Heads of Department provided written informed consent to trial participation before randomisation of their centre.

We conducted the trial from 1 Oct 2012 to 31 Dec 2013. The Simplified Airway Risk Index (SARI) was implemented as a systematic screening tool for assessing intubation difficulties [15, 16]. Elements of the SARI (BMI, jaw protrusion and Mallampati) have also been shown to be predictive of difficult mask ventilation. Four additional and independent risk factors for difficult mask ventilation were assessed in intervention departments (see below). We have addressed the impact of implementing a screening tool for difficult intubation in a separate publication [17], this current paper exclusively addresses the issues of predicting difficult mask ventilation and combined difficulties with mask ventilation and intubation. The two publications include overlapping patients in regard to those being both mask ventilated and tracheally intubated. However, this population, and its related outcome measures, has not previously been described.

The trial was approved by The Danish Data Protection Agency and was exempted from the ethical committee system since it was labelled a quality assurance project [16].

A detailed statistical analysis plan for the intubation part was published before data extraction [16, 18]. The statistical analyses used in this paper adhere to the same principles outlined for the intubation paper [17, 18]. Trial reporting adheres to the 'CONSORT statement: extension to cluster randomised trials' [19].

In the intervention group, all patients were airway-assessed using the defined predictors for difficult airway management: (1) facial beard [7, 8, 10, 11]; (2) snoring [7, 10]; (3) history of sleep apnoea [7, 8, 11]; (4) neck radiation changes [8, 11]; (5) mouth opening [15, 20]; (6) thyromental distance [11, 17, 21]; (7) modified Mallampati classification [7, 8, 11, 17, 21]; (8) neck movement [11, 15]; (9) ability to extend lower jaw [7, 11, 15]; (10) weight [15]; and (11) history of difficult intubation [15, 21]. Repeated educational sessions (tutorial aids, videos, posters, cognitive aids etc.) reinforced compliance with the policy. All variables were recorded pre-operatively and entered into the Danish Anaesthesia

Database (https://www.regionh.dk/kliniskedatabaser/rkkp-databaser/Sider/Dansk-Anaestesi-Database-DAD.aspx) [22]. The database had existed for over a decade before we initiated the trial, but required updating for difficult airway assessment risk factors. During the trial, we reprogrammed the database so it was mandatory to register the eleven risk factors but only in the intervention departments. The control departments (see below) continued their previous registration without any alteration. They answered only the two yes/no questions that pre-existed in the database (on whether facemask ventilation and laryngocopy, respectively, were anticipated difficult), but had no option of reading or registering the eleven risk factors.

The control departments continued existing standards for pre-operative airway assessment, which was left broadly to the individual anaesthetist's discretion. In a survey conducted before the start of the trial, all departments stated that they had no departmental standards for assessing the risk of difficult mask ventilation [23]. These departments had between one to six risk factors for difficult intubation pre-printed on the anaesthesia record, thus encouraging some kind of personal pre-operative airway assessment [23]. None of the departments had specific risk factors for difficult mask ventilation pre-printed on the anaesthesia record. The control departments were not able to record (or view) any risk factors in the Danish Anaesthesia Database (see above).

Outcome assessment was based on data recorded in the Danish Anaesthesia Database, a well-integrated quality insurance database containing quantifiable indicators, covering the peri-operative period. Regardless of trial group, all anaesthetists had to tick the Yes/No boxes to answer two mandatory questions before anaesthesia regarding prediction of difficult mask ventilation and difficult intubation. Furthermore, the anaesthetists recorded an airway management plan pre-operatively (Fig. 1).

Before the trial began, the database was programmed so the intervention departments could record the pre-operative airway assessment consisting of the aforementioned eleven risk factors for difficult airway management in addition to the anaesthetist's anticipation of mask ventilation and intubation difficulties (Yes/No). No risk factors could be recorded into the database in control departments. Immediately following airway management, the anaesthetists recorded the actual circumstances regarding mask ventilation and intubation (Fig. 1).

The anaesthetists graded mask ventilation as easy, difficult or impossible, which is a simplification of the grading scale originally proposed by Han et al. [24] (Fig. 1). In the Danish Anaesthesia Database, grades 1 and 2 from Han's original scale are merged into grade 1 (easy), whereas Han's grades 3 and 4 are respectively identical with the Danish Anaesthesia Database's grade 2 (difficult) and 3 (impossible). Since past cohort studies have focused on difficult and impossible mask ventilation (Han's grade 3 and 4), the results from this trial may be comparable [7, 8, 11, 24].

Patients were categorised as difficult to intubate in the case of three or more intubation attempts or failed intubation, regardless of technique; or, if a change in technique from direct laryngoscopy to an advanced technique, then difficulty was classed after two attempts (Fig. 1).

We regarded combined difficult mask ventilation and difficult intubation as 'unpredicted' if the anaesthetist had failed to predict either difficult mask ventilation or difficult tracheal intubation, or both.

The primary outcomes were: (1) the overall proportion of unpredicted difficult mask ventilation in intervention vs. control groups; (2) the overall proportion of easy mask ventilation, 'falsely predicted difficult' (these being patients predicted as difficult who turned out in fact to be easy; 'false positives').

The secondary outcomes were: (3) the proportion of all actual difficult mask ventilations that were unpredicted in the two groups; (4) for each of the intervention and control groups, the respective sensitivity; specificity; positive and negative predictive values; and positive and negative likelihood ratios.

Exploratory outcomes were: (5) the overall proportion of combined unpredicted difficult mask ventilation coupled with unpredicted difficult intubation; and (6) the overall proportion of combined unpredicted impossible mask ventilation coupled with unpredicted failed intubation.

The pre-trial sample size estimation was performed for the intubation part of the trial and based on the outcome 'unpredicted difficult intubation', as described in our previous papers [16–18]. After the

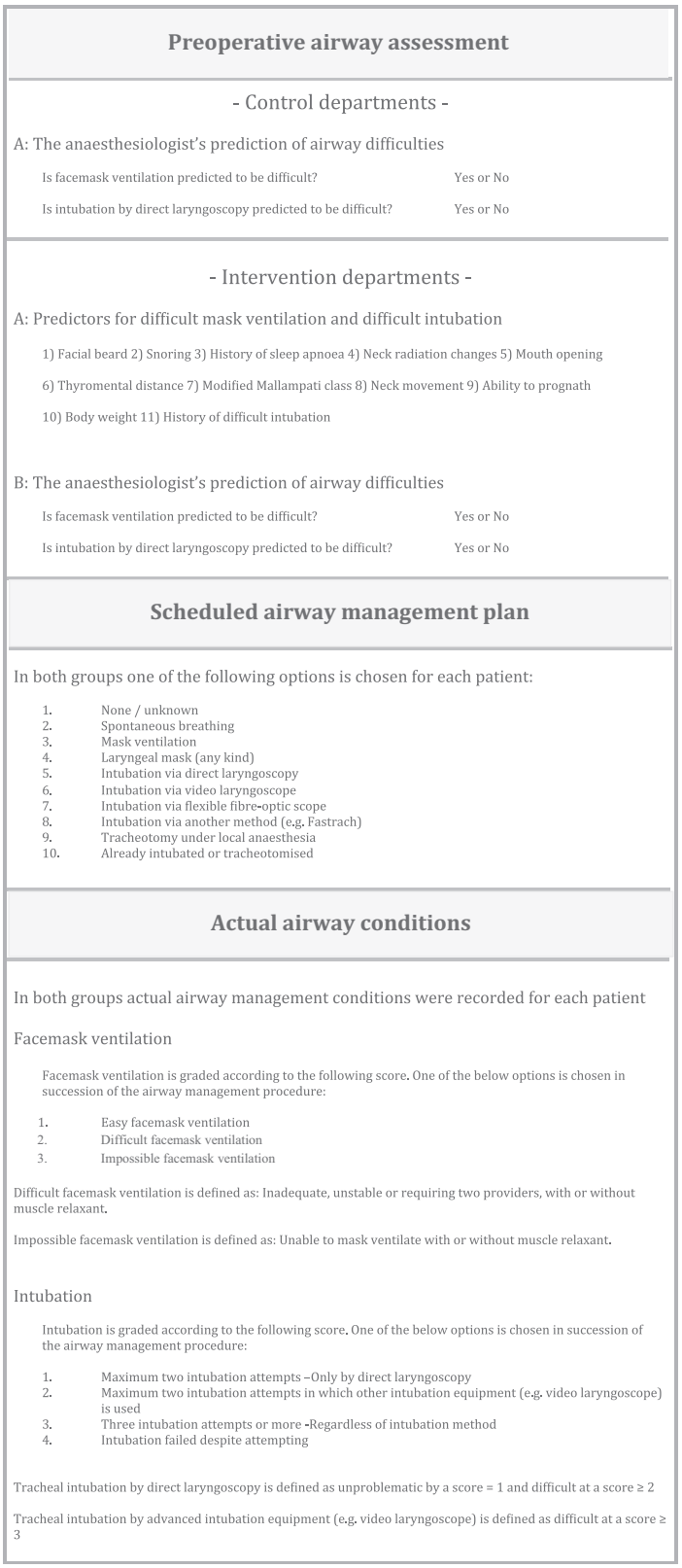

Figure 1 Mandatory data registered in the Danish Anaesthesia Database. Registration of pre-operative airway assessment differed in the intervention and control departments.

trial, we performed power estimation for the mask ventilation part using 'unpredicted difficult mask ventilation' as the primary outcome. As we used cluster randomisation, further calculations were needed to account for the fact that within a cluster, observations tend to be correlated (i.e. non-independent). The sample size required thus depends on average cluster size and the degree of correlation within clusters, ρ, also known as the intracluster correlation coefficient (ICC); we used a value of 0.002 [19].

Using the observed incidence of unpredicted difficult mask ventilation in the control group (0.9%), having 26 participating departments and an average cluster size of 3600 patients, we would be able to detect or reject

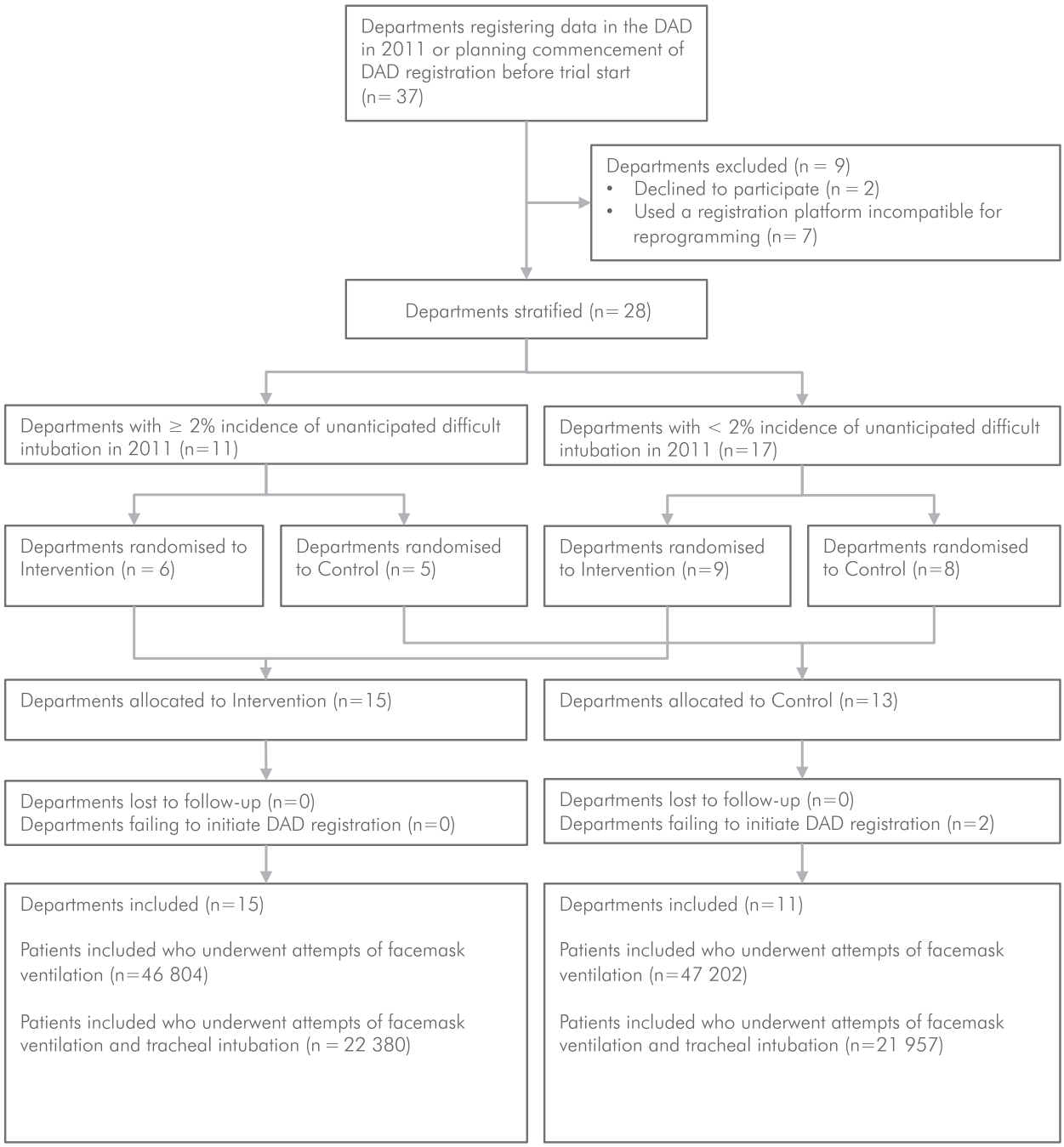

Figure 2 Flow diagram of cluster and patient allocation. DAD, Danish Anaesthesia Database.

a relative risk reduction of 33% with a power of 80%, accepting a risk of type-1 error of 5%. Therefore, the trial was powered to address what we considered a clinically relevant risk reduction. We expressed our main results in terms of an odds ratio, which is an index of the odds of experiencing the outcome (e.g. an unpredicted difficult mask ventilation) in the intervention group vs. the control group (with confidence intervals).

Similar to our previous paper, the analyses were carried out using generalised estimating equations in order to account for the design variables, such as the clustered nature of data and the stratification of departments into strata of high and low baseline incidence of unpredicted difficult intubation [25–27]. Using generalised estimating equations an adjusted odds ratio (OR) between the two groups were attained for relevant outcome measure. IBM SPSS Statistics, Version 22.0., Armonk, NY, USA were used for statistical analyses.

Results

Two control departments did not initiate the Danish Anaesthesia Database registration in time for the study and were excluded, giving a total number of 26 included clusters (15 intervention and 11 control departments) (Fig. 2).

Intervention departments included 46,804 patients, whereas the control departments included 47,202 patients. Baseline characteristics of clusters and patients are presented in Tables 1 and 2. In both groups we had complete data on all variables needed for all outcome measures. In intervention departments, the registration of all individual risk factors was complete in 69% of patients who underwent mask ventilation and 73% of patients who underwent both mask ventilation and tracheal intubation (only registered in intervention group).

The overall proportion of patients who were predicted difficult to mask ventilate was higher in the intervention group (n = 366; 0.78 (0.70–0.86)%) compared with the control group (n = 204; 0.43 (0.37–0.49)%); OR was 1.51 (1.00–2.28), p = 0.049.

Concerning our primary outcome, difficult mask ventilation was unpredicted in 427 (0.91 (0.83–1.00)%) patients in the intervention group and 414 patients (0.88 (0.80–0.97)%) in the control group (Fig. 3); OR 0.98 (0.66–1.44), p = 0.90 (Fig. 4).

The proportion of patients predicted being difficult to mask ventilate, but in fact found to be easy ('falsely predicted difficult') was 0.64 (0.57–0.72)% (n = 298) in the intervention group vs. 0.35 (0.30–

Table 1 Cluster-level summaries. Values are median (IQR [range]) or number (proportion).

Characteristics	Intervention departments 15 clusters	Control departments 11 clusters
Number of patients attempted mask ventilated	2961 (1216–3653 [475–8994])	3620 (1491–6077 [305–10,472])
Number of patients attempted intubated and mask ventilated	1165 (303–1962 [53–5895])	2004 (162–2971 [74–4914])
Fraction of unpredicted difficult mask ventilation in patients attempted mask ventilated	0.8 (0.2–1.0 [0.0–1.4])	0.8 (0.1–0.9 [0.0–1.6])
Fraction of unpredicted easy mask ventilation in patients attempted mask ventilated	0.4 (0.2–0.7 [0.0–1.0])	0.3 (0.2–0.4 [0.0–0.6])
Fraction of combined unpredicted difficult mask ventilation and difficult intubation in patients attempted mask ventilated and intubated	0.2 (0.0–0.3 [0.0–0.5])	0.2 (0.0–0.3 [0.0–0.5])
Age; years	52 (47–55 [42–58])	52 (48–61 [41–65])
BMI; $kg.m^{-2}$	25.3 (24.8–25.7 [23.8–25.9])	25.5 (25.1–25.7 [24.6–26.2])
ASA physical status	2 (1–2 [1–2])	2 (1–2 [1–3])
Private hospitals	4 (27%)	2 (18%)
Stratum 'high' (≥ 2% unpredicted difficult intubations at baseline, 2011)	6 (40%)	5 (45%)
Departments with Ear-Nose-Throat surgery	7 (47%)	6 (55%)

Table 2 Individual participant-level summaries. Values are median (IQR [range]) or number (proportion).

Characteristics	Intervention group n = 46,804	Control group n = 47,202
Sex		
Female	26,663 (57.0%)	24,705 (52.3%)
Male	20,141 (43.0%)	22,497 (47.7%)
Age; years	52 (38–66 [15–89])	56 (40–69 [15–112])
Height; cm	172 (165–179)	172 (165–179)
Weight; kg	75 (65–86 [16–186])	75 (65–87 [17–197])
BMI; $kg.m^{-2}$	25.0 (22.4–28.4 [8.5–97.1])	25.2 (22.6–28.6 [9.7–100.0])
ASA physical status		
1	22,669 (48.4%)	18,774 (39.8%)
2	19,807 (42.3%)	20,188 (42.8%)
3	3840 (8.2%)	7358 (15.6%)
4	173 (0.4%)	690 (1.5%)
5	5 (0.0%)	36 (0.1%)
Unknown	310 (0.7%)	156 (0.3%)
Predicted difficult to mask ventilate		
Yes	366 (0.8%)	204 (0.4%)
No	46,438 (99.2%)	46,998 (99.6%)
Predicted difficult to intubate		
Yes	967 (2.1%)	743 (1.6%)
No	45,837 (97.9%)	46,459 (98.4%)
Scheduled airway management plan		
None/Unknown	669 (1.4%)	85 (0.2%)
Spontaneous breathing	607 (1.3%)	328 (0.7%)
Mask ventilation	2484 (5.3%)	2134 (4.5%)
Supraglottic airway	21,857 (46.7%)	23,704 (50.2%)
Intubation with direct laryngoscopy	18,625 (39.8%)	19,634 (41.6%)
Intubation with other methods	70 (0.1%)	92 (0.2%)
Intubation with videolaryngoscope	1838 (3.9%)	1106 (2.3%)
Tracheostomy under local anaesthesia	1 (0.0%)	1 (0.0%)
Fibreoptic intubation	653 (1.4%)	118 (0.2%)
Priority		
Elective	38,369 (82.0%)	39,841 (84.4%)
Emergency	8419 (18.0%)	7329 (15.5%)
Missing	16 (0.0%)	32 (0.1%)
Mask ventilation		
Easy	46,309 (98.9%)	46,748 (99.0%)
Difficult	473 (1.0%)	444 (0.9%)
Impossible	22 (0.0%)	10 (0.0%)
Neuromuscular blocking agent used during anaesthesia		
Not given	29,819 (63.7%)	27,659 (58.6%)
Non-depolarising	13,813 (29.5%)	16,633 (35.2%)
Depolarising	2403 (5.1%)	2469 (5.2%)
Depolarising and non-depolarising	467 (1.0%)	337 (0.7%)
Missing	302 (0.6%)	104 (0.2%)
Stratum		
High (≥ 2% unpredicted difficult intubation at baseline, 2011)	24,573 (52.5%)	24,015 (50.9%)
Low (< 2% unpredicted difficult intubation at baseline, 2011)	22,231 (47.5%)	23,187 (49.1%)

0.41)% (n = 164) in the control group; OR 1.56 (1.01–2.42), p = 0.045.

Of the patients who were found to be difficult to mask ventilate in the intervention group, 495 (1.06 (0.97–1.16)%), the proportion not predicted was 86.3 (83.0–89.0)% n = 427. The control group registered 454 (0.96 (0.88–1.05)%) difficult mask ventilations of which 414 (91.2 (88.2–93.5)%) were unpredicted; OR 0.61 (0.41–0.91), p = 0.016 (Fig. 4).

The sensitivity of the ability to correctly predict difficult mask ventilation was significantly higher in the intervention group (13.7%) vs. the control group

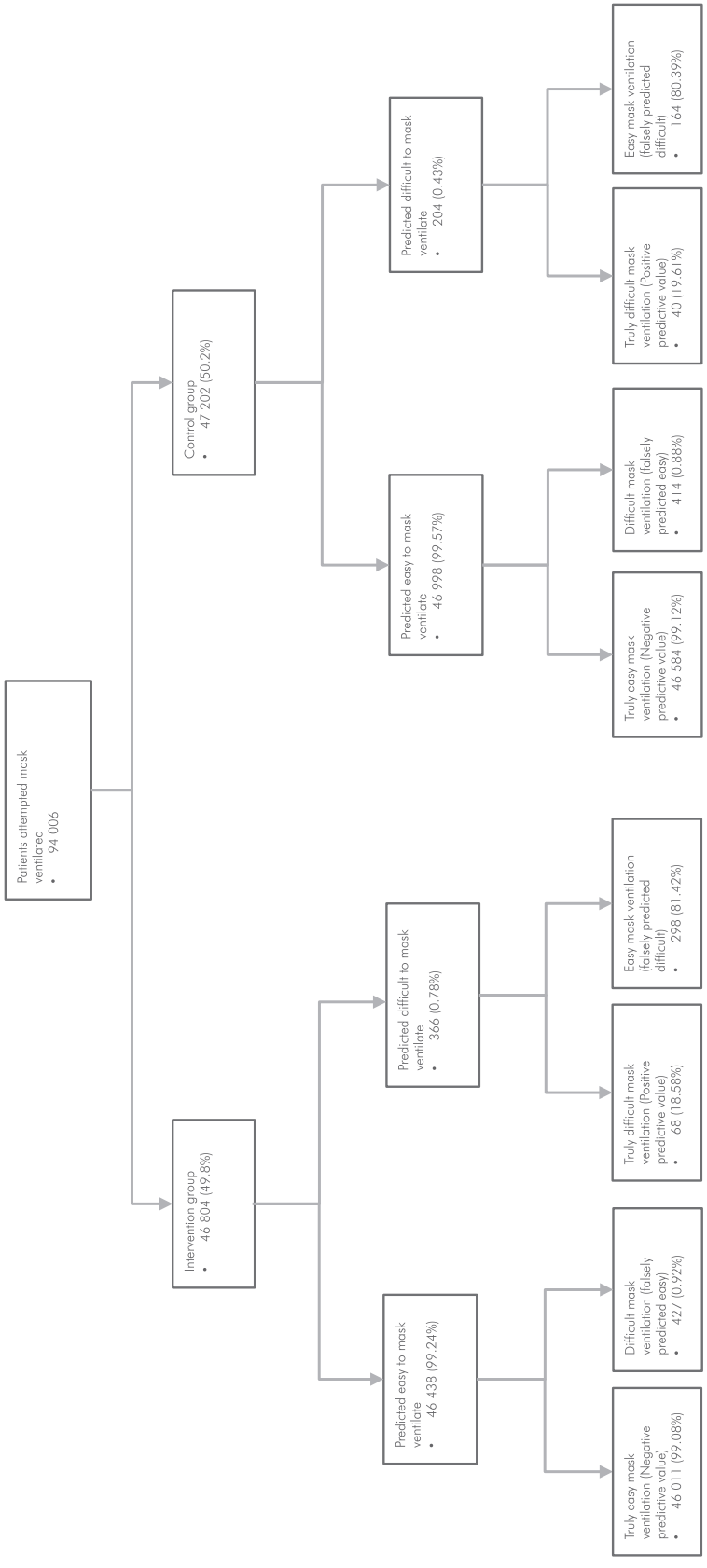

Figure 3 Flow chart in patients in whom mask ventilation was attempted.

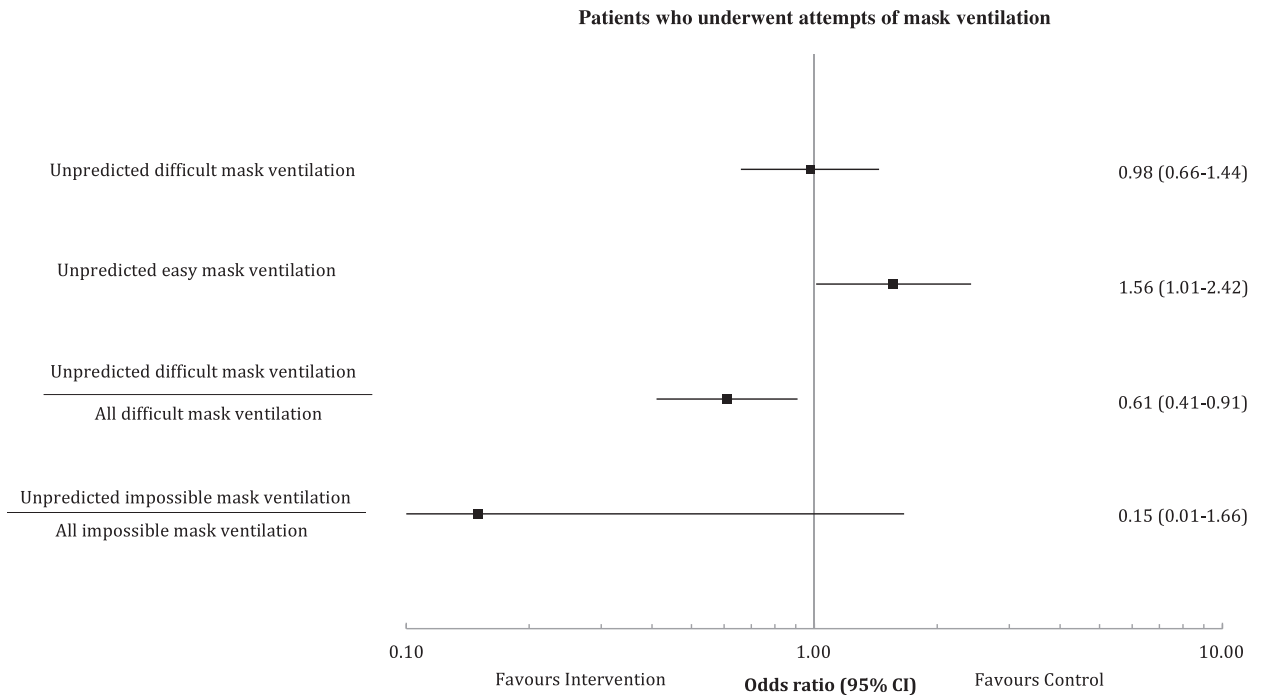

Figure 4 Forest plot of OR (95% CIs) for patients attempted mask ventilated.

(8.8%), p = 0.016. However, no statistically significant differences were detected for specificity, positive and negative predictive values, or positive and negative likelihood ratios between the two trial groups (Table 3).

In the intervention group, 22 patients (0.05 (0.03–0.07)%) vs. 10 (0.02 (0.01–0.04)%) in the control group had impossible mask ventilation and 18 of 22 vs. 9 of 10 were not predicted to be impossible in the intervention and control group, respectively.

We identified 44,337 patients who in whom tracheal intubation was attempted as who were also ventilated with a facemask; 22,380 in the intervention group and 21,957 controls. The proportion of patients who were difficult to intubate were 3.2 (2.9–3.4)% in the intervention group vs. 3.4 (3.2–3.7)% in the control group, and failed intubation occurred in 0.1% in both groups.

The proportion of patients who were difficult to mask ventilate among intubated patients was 1.6 (1.5–1.8)% vs. 1.5 (1.3–1.6)%, in the intervention and control group, respectively. Thus, a higher proportion was difficult to mask ventilate in both groups, when identifying the patients who were also intubated. In the intervention group, 71 of 365 (19.5 (15.7–23.8)%) who were difficult to mask ventilate were also difficult to intubate vs. 65 of 318 (20.4 (16.4–25.2)%) in the control group (Fig. 5). Three of 365 (0.8%) vs. 4 of 318 (1.3%) also had a failed intubation, underlining an association between difficult mask ventilation and difficult/failed intubation in both groups. The incidence of combined difficult mask ventilation and difficult intubation was 0.3% in both groups. Of patients with combined difficulties 78.9 (68.0–86.8)% were unpredicted in the intervention group compared with 81.5 (70.5–89.1)% in the control group (Fig. 3), the OR between the groups was 0.76 (0.41–1.41), p = 0.39 (Fig. 6).

Discussion

Although implementation of a systematic predictive tool led to a higher rate for predicting difficult mask ventilation, there remained an equal proportion of unpredicted difficult mask ventilation in the intervention and control groups. Perhaps as a consequence of the higher prediction rate, the proportion of 'falsely predicted difficult' mask ventilations increased in the intervention group. However, of the patients who were found to be difficult to mask ventilate, the proportion predicted in the intervention group was higher than in the control group. This result is arguably the most important for airway management. Although the results for the intervention do not reach conventional thresholds for specificity, positive and negative predictive

Table 3 Accuracy of predicting difficult mask ventilation and combined difficult mask ventilation and intubation. Values are number (proportion).

	Intervention group		Control group	
	n = 46,804	95% CI	n = 47,202	95% CI
Prediction of difficult mask ventilation				
Total patients	46,804		47,202	
Predicted difficult (positive)	366		204	
True positive (predicted and actually difficult)	68		40	
False positive (predicted difficult, but actually easy)	298		164	
Predicted easy (negative)	46,438		46,998	
True negative (predicted easy and actually easy)	46,011		46,584	
False negative (predicted easy and actually difficult)	427		414	
Sensitivity	13.7%	(10.9–17.2)	8.8%	(6.4–11.9)
Specificity	99.4%	(99.3–99.4)	99.6%	(99.6–99.7)
Positive predictive value	18.6%	(14.8–23.0)	19.6%	(14.5–25.9)
Negative predictive value	99.1%	(99.0–99.2)	99.1%	(99.0–99.2)
Positive likelihood ratio	21.3	(16.7–27.4)	25.1	(18.0–35.0)
Negative likelihood ratio	0.9	(0.8–0.9)	0.9	(0.9–0.9)
Prediction of difficult mask ventilation and intubation				
Total patients	22,380		21,957	
Predicted DMV and/or DTI (positive)	956		646	
True positive (predicted and actually difficult)	15		12	
False positive (predicted difficult, but actually easy)	941		634	
Predicted easy MV and TI (negative)	21,424		21,311	
True negative (predicted easy and actually easy)	21,368		21,258	
False negative (predicted easy and actually difficult)	56		53	
Sensitivity	21.1%	(12.7–32.7)	18.5%	(10.3–30.4)
Specificity	95.8%	(95.5–96.0)	97.1%	(96.8–97.3)
Positive predictive value	1.6%	(0.9–2.6)	1.9%	(1.0–3.3)
Negative predictive value	99.7%	(99.7–99.8)	99.7%	(99.7–99.8)
Positive likelihood ratio	5.0	(3.2–7.9)	6.4	(3.8–10.7)
Negative likelihood ratio	0.8	(0.7–0.9)	0.8	(0.7–0.9)

CI, confidence intervals; DMV, difficult mask ventilation; DTI, difficult tracheal intubation.

values, safety rests on the avoidance of unpredicted difficult situations, as it is these that can lead to harm.

Moreover, our data revealed a 20% risk of difficult intubation in both groups when already faced with difficult mask ventilation, reconfirming the association found in earlier observational studies [9, 11].

This is probably the first randomised clinical trial addressing the effects of using systematic assessment of risk factors for difficult mask ventilation.

Even though all departments stated that they registered no risk factors for mask ventilation difficulties, it is important to emphasise that practice in the control group was not 'no airway assessment at all'. If clinical practice for individual anaesthetists in the control group was of high quality then it may have approximated practice in the intervention centres by default, contributing to a dilution of the intervention effect.

Our trial has a number of other potential limitations. First, in the intervention group, it is possible practitioners were 'sensitised' to the possibility of difficult mask ventilation, so reporting of this was higher as a consequence. Second, our sample size estimation was based on a previous paper, which used the incidence of unpredicted difficult intubation, and not difficult mask ventilation. However, considerably more patients were mask ventilated than intubated during the trial period, hereby increasing the number of patients included and the statistical power for this part of the trial. Power estimation suggested that the trial had a power of 80% to detect or reject a 33% relative risk difference in the numbers of unpredicted difficult mask ventilations between the groups. Even though the number of patients in each trial group was almost perfectly balanced, the case-mix was slightly uneven. However, our use of generalised estimating equation modelling took this into account.

We adjusted our results for use of neuromuscular blocking agents (NMB). However, the mask ventilation

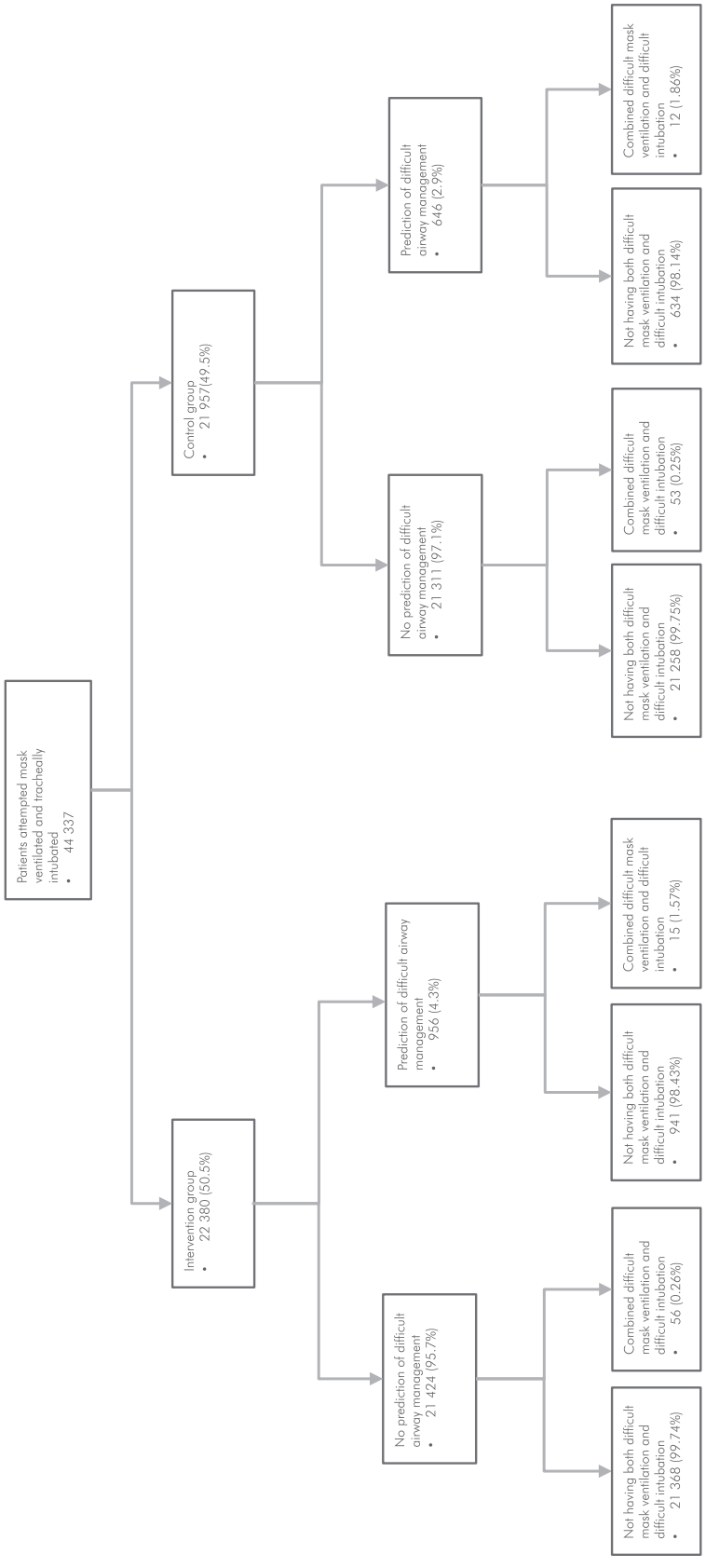

Figure 5 Flow chart of results of patients in whom mask ventilation and tracheal intubation was attempted.

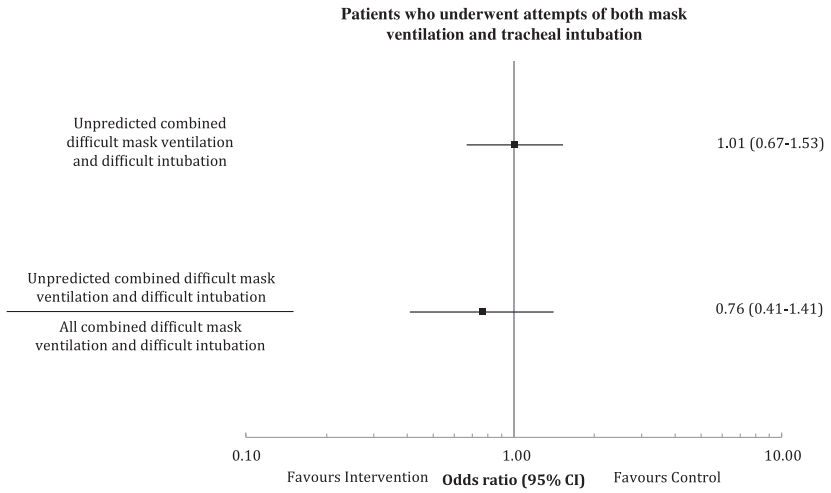

Figure 6 Forest plot of OR (95% CIs) for patients in whom mask ventilation and tracheal intubation was attempted.

score from the Danish Anaesthesia Database did not allow us to differentiate between use and avoidance of NMB specifically for airway management. It would have been of interest had we been able to address the use of NMB before or after attempts of mask ventilation, especially in difficult mask ventilation [28, 29]. In turn, this might have influenced the degree of difficulty perceived, although we have no reason to believe that this potential influence would have been unevenly distributed between trial groups.

The overall proportion of unpredicted difficult mask ventilation was not reduced in the intervention group; the proportion of unpredicted difficulties remained very high (86% and 91% in the two groups). There remains a challenge to improve the diagnostic accuracy of airway prediction.

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Competing interests

Before the trial began, a peer-reviewed protocol was published and made available on http://www.clinicaltrials.gov (NCT01718561) [16]. No authors declare any financial relationships with any organisations that might have an interest in the submitted work or other relationships or activities that could appear to have influenced the submitted work. AN received research grants from the TRYG foundation as part of his PhD study for the submitted work. The trial was funded by independent grants from the TRYG foundation; Nordsjællands Hospitals research council; the National Research Council of Denmark; the Capital Regions funds for research; and the DASAIMs fund. The funding entities had no influence on the trial design, conduction or reporting. The research group is independent from the funders.

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Appendix

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