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Is there a relationship between anaesthesia and dementia?

Anna-Karin Strand¹, Fredrik Nyqvist², Anne Ekdahl³, Gun Wingren⁴, Christina Eintrei⁵

Short title: Anaesthesia and dementia

¹MD, DESA, Division of Anaesthesia, Department of Medical and Health Sciences, Linköping University, Sweden.

²Bsc, Department of Clinical and Experimental Medicine, Occupational and Environmental Medicine, Faculty of Medicine and Health Sciences, Linköping University, Sweden.

³MD, PhD, Department of Neurobiology, Care Sciences and Society (NVS), Division of Clinical geriatrics, Karolinska Institutet (KI) and Department of Clinical Sciences Helsingborg, Lund University, Sweden.

⁴Associate Professor, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden.

⁵Professor, MD, PhD, Division of Anaesthesia, Department of Medical and Health Sciences, Linköping University, Sweden.

Corresponding author: Prof Christina Eintrei, Div. of Anaesthesia, Dept. of Medical and Health Sciences, Linköping University, 581 85 Linköping, Sweden

christina.eintrei@liu.se

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Abstract

Background

Long-term cognitive problems are common among elderly patients after surgery, and it has been suggested that inhalation anaesthetics play a role in the development of dementia. This study aims to investigate the hypothesis that patients with dementia have been more exposed to surgery and inhalational anaesthetics than individuals without dementia.

Methods

Using 457 cases from a dementia-registry and 420 dementia-free controls, we performed a retrospective case-control study. The medical records were reviewed to determine exposure to anaesthesia occurring within a 20-year timeframe before the diagnosis or inclusion in the study. Data were analysed using multivariate logistic regression and propensity score analysis.

Results

Advanced age (70 years and older, with the highest risk in ages 80 to 84 years) and previous head trauma were risk factors for dementia. History of exposure to surgery with anaesthesia was a risk factor for dementia (OR = 2.23, 95% CI 1.66-3.00, $P < 0.01$). Exposure to inhalational anaesthetics with halogenated anaesthetics was associated with an increased risk of dementia, compared to no exposure to anaesthesia (OR = 2.47, 95% CI 1.17-5.22, $P = 0.02$). Exposure to regional anaesthesia was not significantly associated with increased risk of dementia ($P=0.13$).

Conclusion

In this 20-year retrospective case-control study, we found a potential association between dementia and prior anaesthesia. Exposure to general anaesthetics with halogenated anaesthetic gases was associated with an increased risk of dementia.

Introduction

Initially identified after cardiac surgery ¹, postoperative cognitive dysfunction (POCD) has been commonly described among elderly patients also after non-cardiac surgery ² and has been found to correlate with higher long-term morbidity and mortality ³⁻⁵. Also, histological pathologies mimicking those of Alzheimer's disease (AD) have been observed in animals and human brain cells when exposed to inhalation anaesthetics ^{6,7}, and the human neuro-inflammatory response to surgery and anaesthesia has been found to resemble AD ^{8,9}. The possible relationship between anaesthesia, POCD and dementia remains elusive ¹⁰⁻¹⁵, but studies have shown an increased risk of cognitive decline after anaesthesia and surgery ¹⁶, and it has been suggested that inhalation anaesthetics may play a part in the development of dementia ¹⁷⁻¹⁹. There are studies suggesting an increased risk for dementia in elderly patients after exposure to general anaesthesia. ^{16,20}

Despite these concerns, research on anaesthesia and dementia is sparse; most previous publications have not approached this specific subject but have rather identified anaesthesia as one factor among many others in epidemiologic studies. Also, few, if any, researchers have studied exposure occurring more than five years before diagnosis. A meta-analysis in 2011 ²¹ and an international workshop in 2009 ²² concluded that more studies were needed in this field.

Hypothesis:

Sentence excluded. We set the hypothesis that exposure to inhalational anaesthetics with halogenated gas leads to increased risk of dementia. Sentence excluded. This study compares patients with diagnosed dementia to a control group regarding exposure to surgery and anaesthesia.

Methods

Study design and participants

We performed a retrospective case-control study at the Department of Anaesthesiology, Linköping University Hospital, Sweden. The study was performed in accordance with guidelines for the conduct of observational studies²³.

Procedures

Cases were retrieved from the Swedish Dementia Quality Registry (SveDem, www.svedem.se), a national quality register. We obtained all cases registered in the county of Östergötland from May 2007 to April 2012 with diagnoses of AD, late-onset AD (LOAD), early-onset AD (EOAD) and mixed AD/VaD (Mixed Alzheimer's and vascular dementia). Three individuals with Mb Down were excluded, leaving 457 cases for inclusion in the study²⁴. These were the total number of available cases in Östergötland from the Dementia registry during this time period.

Dementia-free controls were obtained from Statistics Sweden (www.scb.se) in a process whereby individuals were asked to take part as plausible controls in the study (according to Swedish law). Due to this process, 420 controls were retrieved from an initial sampling frame of 104 703 individuals. The procedure leading to the final control group is described in figure 1. Controls for which the review of medical records discovered a diagnosis of dementia or pronounced cognitive decline were excluded. An experienced geriatrician was consulted in this procedure. Both cases and controls were inhabitants in the county of Östergötland and could be dead or alive at the inclusion date.

Ethics

The study was approved by the regional Ethical Committee of Linköping (c/o the medical faculty office, 2:nd floor, University of Linköping, 581 83 Linköping, Sweden, d-nr 2012/30-31, amendments 2012/307-32, 2012/369-32 and 2012/193-31). The SveDem registry operates within the legal framework of Swedish national health registries.

Statistical analysis

In the analyses, both cases and controls have an inclusion date variable. For the cases, this is the date of dementia diagnosis, while the controls were assigned a generated inclusion year with a matching year distribution. This is used as a time reference for calculating risk for different exposures occurring within a 20-year retrospective time frame.

For all cases and controls, medical records dating back 20 years from the inclusion year were retrieved and examined by research nurses with special education in anaesthesia and/or intensive care. Previous illness, such as diabetes, head trauma, cerebrovascular disease and exposure to cardiopulmonary bypass, were noted.

Exposure was defined as the number, duration and types of anaesthesia exposure. For each exposure to anaesthesia, the agents used for induction and maintenance were noted, as well as any of the following adverse events: hypotension (systolic blood pressure lower than 80 mm Hg or more than 30% below the baseline value for five minutes or more), hypoxia (arterial oxygen saturation below 90% for two minutes or more), tachycardia (an increase of 30 beats per minute or more from baseline for five minutes or more or any new arrhythmia) and days in hospital.

The types of regional anaesthesia (RA) were spinal, epidural or peripheral nerve blocks used for surgery, with or without sedation. General anaesthesia without gas (GA no gas) included all kinds of intravenous maintenance of anaesthesia. General anaesthesia with gas (GA gas) included any exposure to maintenance with halogenated anaesthetic gases, thus excluding

nitrous oxide. Any surgery with exposure to halogenated anaesthetic gases was considered as GA with gas.

Descriptive analyses were performed, including all subjects, for a comparison of demographics, previous diseases and information from performed surgeries. Since age is known to be an important risk factor, subjects were divided into six age categories of five-year intervals.

T-tests were used for analyses of continuous variables, and cross tabulated chi-square tests were used for categorical variables. Analyses were performed using SPSS software. A p-value < 0.05 was considered statistically significant.

To investigate whether anaesthesia exposure was related to dementia diagnosis, the data were analysed through logistical regression models.

Since the cases and controls had different age distribution and age is a strong risk factor for dementia we used propensity score analysis to adjust for the differences. The propensity score analysis used a model with anaesthesia as dependent variable and age as independent, only subjects within the common support range was included (439 cases and 416 controls). A logistic regression model, with the propensity score included, was performed thereafter. In the model other potential confounding factors was included. The variables included were those that were statistically significant in the univariate model or were of clinical or biological significance (gender, hypotension, type of anaesthesia, number of exposures and total time of anaesthesia). To compensate for the variation in the ongoing surgery time between the different observations, we also included total time of anaesthesia in the multivariate model. Exposure to anaesthesia, with different methods (RA, GA without gas and GA with gas), within 20 years prior to diagnosis was compared against no such exposure. We noted that a history of head trauma was overrepresented amongst the cases, and therefore, we repeated the

multivariate analyses, excluding all individuals with previous head trauma (18 cases and 4 controls). All regression models were performed in the software STATA 14 (Statistical Software StataCorp LP, US).

Results

A total of 457 cases and 420 controls were included in the analyses. Data was collected between April 2012 and May 2015. The demographics are described in table 1. Relative to the control group, those in the dementia group were older (82 years v. 77 years, $P < 0.01$).

Traumatic head injury was more common among dementia cases ($P = 0.01$). There was no significant difference between cases and controls regarding prevalence of other comorbidities (diabetes, cerebrovascular disease or previous exposure to heart-lung machine). The dementia types were mainly LOAD (56%) and mixed AD/VaD (31%). A smaller proportion had EOAD (13%).

More cases than controls had been exposed to anaesthesia within a 20-year time frame (39% v. 22%, $P < 0.01$). Hypotension during anaesthesia was more common among cases (21% v. 13%, $P < 0.01$). Hypoxia during anaesthesia occurred in three cases and one control, and was not further analysed. No difference in the mean duration of anaesthesia (83 v. 94 min, $P = 0.27$) or accumulated mean time in the hospital related to anaesthetic exposure were found (2.6 v. 2.1 days, $P = 0.28$). A majority of the individuals in the study had records of one or two exposures to anaesthesia, but some had as many as 11 surgical procedures with anaesthesia (fig 2). The cases were more exposed to all types of anaesthesia (fig 3). Descriptive data of the deceased and living controls are presented in supplement 1.

Logistic regression analyses

The logistic regression models are shown in table 2. A history of head trauma was strongly associated with increased risk of dementia (unadjusted OR = 4.26, 95% CI 1.43-12.70, $P = 0.01$), and all the results were consistent when these individuals were excluded from the multivariate model.

When adjusted for other variables in the multivariate model (age, gender, hypotension, type of anaesthesia, number of exposures and total time of anaesthesia), we found that advanced age (70 years and above) was the strongest risk factor for dementia, with the highest risk in ages 80 to 84 (OR = 6.74, 95% CI 3.87-11.75, $P < 0.01$). Female gender was not associated with a significant increase in the risk of dementia (OR = 1.19, 95% CI 0.88-1.61, $P = 0.26$).

Any exposure to surgery with anaesthesia yielded an increased risk of dementia (OR = 2.23, 95% CI 1.66-3.00, $P < 0.01$). It seemed that the risk of dementia increased with number of exposures, with the highest risk after three or more exposures (OR = 6.39, 95% CI 2.44-16.73, $P < 0.01$) but this result was not consistent when propensity score analysis was used (suppl 2).

Exposure to inhalational anaesthetic with halogenated gas was associated with an increased risk of dementia, compared to no exposure to anaesthesia (OR = 2.47, 95% CI 1.17-5.22, $P = 0.02$), whereas other types of anaesthesia (RA and GA no gas) were not associated with a significantly higher risk of dementia when adjusted for other significant variables (OR = 1.82, 95% CI 0.83-3.98 $P = 0.13$ and OR = 1.18, 95% CI 0.48-2.91 $P = 0.72$). When propensity score analysis was used, exposure to both inhalational and regional anaesthesia was associated with increased risk of dementia (suppl 2). Also, when adjusted for other significant variables, hypotension was not associated with an increased risk of dementia (OR = 1.21, 95% CI 0.67-2.19 $P = 0.52$). These results came out similar when propensity score analysis was used (suppl 2).

Discussion

In this retrospective case-control study of 877 individuals, we found that the dementia group was more exposed to anaesthesia previously in life than the dementia-free group. Exposure to general anaesthesia with halogenated anaesthetic gases was found to be a risk factor for dementia in this cohort, whereas other types of general anaesthesia were not. The accumulated total time of anaesthesia did not increase the risk of dementia. Many of the cases were exposed to regional anaesthesia, which may be explained by several factors; orthopaedic trauma, fragile elderly patient, cognitive decline etc. Others have found an association between exposure regional aesthesia and dementia¹⁶ but in our study, regional anaesthesia was not associated with increased dementia risk when analysed with logistic regression.

Although this study has limitations which make it difficult to draw reliable conclusions, we will start discussing the results in relation to previous research.

One previous study showed that patients anaesthetized with sevoflurane presented worse results on postoperative cognitive tests compared to those with intravenous maintenance²⁵. That study was based on a short follow up (10 days) and doesn't say anything about long term cognitive deficits, but the results reinforced the possibility that inhalation anaesthetics may play a part in the development of dementia¹⁷⁻¹⁹. Possible mechanisms have been put forward suggesting that inhalational anaesthetics may be neurotoxic and contribute to POCD²⁶. An explanation for the acceleration of Alzheimer's neuropathology by inhaled anaesthetic agents include increased amyloid β oligomerisation and tau phosphorylation and aggregation, as suggested by experimental research on mice^{6,18}.

A history of exposure to organic solvents has been suggested to be associated with an increased risk of Alzheimer's disease²⁷. Halogenated inhalational anaesthetics are molecularly similar to organic solvents and are thus highly fat soluble and could easily affect brain tissue.

Whether the proposed increased dementia risk is related to anaesthesia exposure, and specifically inhalation anaesthesia, or if the surgical process itself plays a role will always be difficult to establish since anaesthesia and surgery are inseparable²⁸. One suggested cause has been that surgery and tissue damage cause impairment of the blood-brain barrier via inflammatory responses, thus causing neuro inflammation and neuronal dysfunction leading to POCD²⁹. There are also newer studies speaking against any risk of long-term cognitive impairment after surgery^{30,31}.

An important consideration is that the burden of medical comorbidity in individuals with Alzheimer's disease is greater than in individuals without dementia, which might cause these patients to be more prone to surgery and influence the anaesthetic method. The overrepresentation of inhalation anaesthesia in our study cases may be attributed to medical conditions or surgery-related factors, although we found no difference in comorbidities, such as diabetes or cerebrovascular disease, between the dementia group and the control group. Another plausible explanation is that events during anaesthesia and surgery may contribute to cerebral damages. We investigated the occurrence of hypotension during anaesthesia and found that it was higher among the dementia group, but adjusted for other variables, hypotension was not associated with increased dementia risk. Hypoxia during anaesthesia was very rare.

We also found that increasing age and a history of traumatic head injury were independent risk factors for dementia, which is well known^{32,33}. Because of the overrepresentation of previous head trauma among the dementia group, we chose to perform multivariate logistic analyses where all individuals with head trauma were excluded, and the results showing increased risk of dementia related to surgery and anaesthesia were consistent without individuals with head trauma.

We propose several explanations of our results: a. Do Propofol protect the brain from dementia? ^{34,35} b. Regional anaesthesia may have been chosen because of the patients medical conditions (more fragile, cognitively affected, elderly, orthopaedic trauma and more comorbidity). c. Is the increased risk of dementia caused by surgery in itself, trauma and hospitalization? Sentence excluded.

Our study aims to investigate an issue where research is sparse but there is a growing interest in this topic, since dementia is increasing worldwide and becomes an economical burden for our societies. Several animal and in vitro cell studies have indicated a potential relationship between inhalation anaesthesia and AD, but reliable results on humans are lacking. Strength of the study is that data was extracted from two registers with high quality, SveDem and the Registry of the total population from Statistics Sweden. The information at the SveDem is mainly provided by memory clinics, which ensures a standardized diagnostic procedure and a high specificity of the different diagnoses of dementia. Controls were retrieved from the same proportion of rural and urban areas as the dementia group to ensure a similar distribution of ways of living, including educational and socioeconomic factors. Medical records were reviewed by highly qualified research nurses. Thanks to the personal identity number and thoroughly kept archives in the Swedish Health Care system, relevant medical information was retrieved for surgeries dating up to 20 years prior to the date of inclusion. Few other epidemiological studies concerning this topic have used such a long exposure time frame prior from the year of diagnosis.

Limitations of the study

There are several limitations of our study. First, it is a retrospective study with a relatively small sample size. It has the same limitations as all studies of medical records; that the contents of medical records are inconsistent due to the long time studied. We reviewed medical records from one Swedish county only; thus, both the dementia and control groups

could possibly have had other exposures to anaesthesia elsewhere in their medical history, which we did not have access to. Little information was provided in the records about pre-existing medical conditions and details concerning the surgical procedures.

Furthermore, the sampling process of the control group comprises several problems. The dementia group and control group were initially matched at group level, but as a result of the procedure in which the control individuals gave their permission to take part in the study (fig 1) there were differences in age and gender distribution between the two groups. The controls were “self-selected” by returning letters in the mail. This procedure was required for ethical reasons but may impose a potential bias which cannot be investigated. It may be that the control group consists of more healthy individuals, who on average would be expected to have been less exposed to surgery and anaesthesia than their less healthy counterparts, thus creating a bias towards less anaesthesia exposure. All analyses were adjusted for age and gender but we cannot adjust for the sampling process. We found that the living controls were generally older than the deceased controls (suppl 1).

Conclusion

In this 20-year retrospective clinical case-control study, the results show a potential association between dementia and exposure to general anaesthesia with halogenated anaesthetics. Exposure to other types of anaesthesia was not associated with dementia-risk. It is difficult to draw reliable conclusions from this study and further studies regarding this topic are warranted.

Abbreviations

AD: Alzheimer's disease; POCD: postoperative cognitive dysfunction; LOAD: late-onset AD; EOAD: early-onset AD; mixed AD/VaD: mixed Alzheimer's and vascular dementia; GA: general anaesthesia; RA: regional anaesthesia; OR: odds ratio; CI: confidence interval; SD: standard deviation.

Author's contribution

AKS participated in designing the study, in collecting, analysing and interpreting the data and was mainly responsible for writing the manuscript. FN participated in analysing and interpreting the data and in writing the manuscript. GW participated in designing the study, in analysing and interpreting the data and in editing the manuscript. AE participated in designing the study, in analysing and interpreting the data and in editing the manuscript. CE participated in designing the study, in analysing and interpreting the data and in editing the manuscript. All authors read and approved the final manuscript.

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Conflict of interests: The authors declare that they have no conflict of interest.

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Table 1. Descriptive	Cases n=457		Controls n=420		Chi-Square/ T-test
	n	% / SD	n	% / SD	P-value
Demographics					
Age (year, mean)	82.0	± 0.4	76.7	± 0.4	<0.01
Gender					
Male	198	43.3	202	48.1	0.16
Female	259	56.7	218	51.9	
Deceased	180	39.4	138	32.9	0.04
Comorbidity					
Diabetes	79	17.3	68	16.2	0.66
Head trauma	18	3.9	4	0.9	<0.01
Stroke/ CVI	42	9.2	29	6.9	0.22
Ever HL-machine	20	4.4	24	5.7	0.37
Data related to Dementia					
Heredity (cases only)	122	26.7	-	-	-
Dementia type (cases only)					
Alzheimer's early onset	58	12.7	-	-	-
Alzheimer's late onset	257	56.2	-	-	-
Mixed Alzheimer's and vascular	142	31.1	-	-	-
Anaesthesia related data					
Any surgery with anaesthesia	179	39.2	94	22.4	<0.01
Number of exposures					
No anaesthesia	278	60.8	326	77.6	<0.01
1	98	17.0	51	12.1	
2	58	9.7	27	6.4	
=>3	23	4.5	16	3.8	
Total time anaesthesia (minutes, mean)	83.11	±167.6	94.4	±136.5	0.27
(minutes, median)	140.0	iqr 85-240	197.5	iqr 120-380	
Hypotension during anaesthesia	97	21.2	55	13.1	<0.01
Hypoxia during anaesthesia	3	-	1	-	-
Type of anaesthesia					
No anaesthesia	278	60.8	326	77.6	
RA	47	10.3	21	5.0	
GA (no gas)	23	5.0	15	3.6	<0.01
GA (gas)	109	23.9	58	13.8	
Hospitalization (days, mean)	2.61	±6.4	2.08	±8.2	0.28

Chi-square test for categorical variables and T-test for continuous variables.

Table 2. Logistic regression		Cases n=457		Controls n=420		A		B	
Variable	n	% / SD	n	% / SD	OR (95% CI)	P-value	OR (95% CI)	P-value	
Any surgery with anaesthesia	179	39.17	94	22.38	2.23 (1.66-3.00)	<0.01			
Anaesthesia									
No anaesthesia	278	60.83	326	77.62	Reference		Reference		
RA	47	10.28	21	5.00	2.62 (1.53-4.50)	<0.01	1.82 (0.83-3.98)	0.13	
GA (no gas)	23	5.03	15	3.57	1.80 (0.92-3.51)	0.09	1.18 (0.48-2.91)	0.72	
GA (gas)	109	23.85	58	13.81	2.20 (1.54-3.15)	<0.01	2.47 (1.17-5.22)	0.02	
Number of exposures									
No anaesthesia	278		326		Reference		Reference		
1	98		51		2.25 (1.55-3.28)	<0.01	1.97 (1.16-3.35)	0.01	
2	58		27		2.52 (1.55-4.09)	<0.01	3.25 (1.53-6.89)	<0.01	
>=3	23		16		1.69 (0.87-3.25)	0.12	6.39 (2.44-16.73)	<0.01	
Total time anaesthesia (mean)	83.11	±167.58	94.36	±136.54	0.99 (0.99-1.00)	0.28	0.99 (0.99-0.99)	<0.01	
Hypotension (under anaesthesia)									
No	360	78.77	365	86.90	Reference		Reference		
Yes	97	21.23	55	13.10	1.79 (1.25-2.57)	<0.01	1.21 (0.67-2.19)	0.52	
Head trauma									
No	439	96.06	416	99.05	Reference		Excluded		
Yes	18	3.94	4	0.95	4.26 (1.43-12.70)	<0.01	-		
Age category									
58-69	36	7.88	99	23.57	Reference		Reference		
70-74	50	10.94	103	24.52	1.33 (0.80-2.22)	0.27	1.27 (0.73-2.19)	0.40	
75-79	75	16.41	72	17.14	2.86 (1.74-4.72)	<0.01	2.98 (1.74-5.11)	<0.01	
80-84	99	21.66	45	10.71	6.05 (3.60-10.17)	<0.01	6.74 (3.87-11.75)	<0.01	
85-89	111	24.29	54	12.86	5.65 (3.42-9.33)	<0.01	5.87 (3.45-10.00)	<0.01	
90+	86	18.82	47	11.19	5.03 (2.99-8.48)	<0.01	4.92 (2.83-9.55)	<0.01	
Gender									
Male	198	43.33	202	48.10	Reference		Reference		
Female	259	56.67	218	51.9	1.21 (0.93-1.58)	0.16	1.19 (0.88-1.61)	0.26	

A= univariate logistic regression model

B= multivariate logistic regression model adjusted for all variables presented in table, excluding individuals with head trauma from analysis

Supplement 1. Descriptive data of deceased and living controls	Deceased n=138		Live n=282		Chi- Square/ T-test P-value
	n	% / SD	n	% / SD	
Demographics					
Age (year, mean)	73.2	± 6.99	83.82	± 7.99	<0.01
Gender					
Male	71	51.44	131	46.45	0.34
Female	67	48.55	151	53.55	
Comorbidity					
Diabetes	37	26.81	101	35.82	<0.01
Head trauma	1	0.72	3	1.06	0.74
Stroke/ CVI	22	15.94	7	0.35	<0.01
Ever HL-machine	12	8.70	12	4.26	0.07

Chi-square test for categorical variables and T-test for continuous variables.

Supplement 2. Propensity score analysis	Cases n=439	Controls n=416
	OR (95% CI)	P-value
Anaesthesia		
RA	2.91 (1.11-7.64)	0.03
GA (no gas)	1.77 (0.61-5.06)	0.29
GA (gas)	2.60 (1.12-6.05)	0.03
Number of exposures		
No anaesthesia	<i>Reference</i>	
1	1.39 (0.64-3.02)	0.41
2	1.61 (0.70-3.69)	0.26
>=3	(omitted)	
Hypotension (under anaesthesia)		
No	<i>Reference</i>	
Yes	0.99 (0.59-1.66)	0.96
Gender		
Male	<i>Reference</i>	
Female	1.29 (0.98-1.71)	0.07
Propensity score	2.14 (1.25-3.67)	0.01

Figure legends

Figure 1. Flow diagram. The procedure leading to the final control group.

Figure 2. Number of exposures to anaesthesia. A majority of the individuals in the study had records of one or two exposures to anaesthesia, but some had as many as 11 surgical procedures with anaesthesia.

Figure 3. Type of anaesthesia. The types of anaesthesia that the individuals in the study had been exposed to.