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Anesthesia properties for hip fracture patients

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Abstract
Hip fracture is a trauma of the elderly. The worldwide number of patients in need of surgery after hip fracture will increase in the coming years. The 30-day mortality ranges between 4 and 14%. Patients' outcome may be improved by anaesthesia technique (general vs. neuraxial anaesthesia). There is a dearth of evidence from randomised studies regarding to the optimal anaesthesia technique. However, several large non-randomised studies addressing this question have been published from the onset of 2010.
Methods: To compare the 30-day mortality rate, in-hospital mortality rate and length of hospital stay after neuraxial (epidural/spinal) or general anaesthesia in hip fracture patients (≥ 18 years old) we prepared a systematic review and meta-analysis. A systematic search for appropriate retrospective observational and prospective randomised studies in Embase and PubMed databases was performed in the time-period from 01.01.2010 to 21.11.2016. Additionally, a forward searching in google scholar, a level one reference list searching and a formal searching of trial registries was performed.
Results: Twenty retrospective observational and three prospective randomised controlled studies were included. There was no difference in the 30-day mortality [OR 0.99; 95% CI (0.94 to 1.04), $p = 0.60$] between the general and the neuraxial anaesthesia group. The in-hospital mortality [OR 0.85; 95% CI (0.76 to 0.95), $p = 0.004$] and the length of hospital stay were significantly shorter in the neuraxial anaesthesia group [MD -0.26; 95% CI (−0.36 to −0.17); $p < 0.00001$].
Conclusion: Neuraxial anaesthesia is associated with a reduced in-hospital mortality and length of hospitalisation. However, type of anaesthesia did not influence the 30-day mortality. In future there is a need for large randomised studies to examine the association between the type of anaesthesia, post-operative complications and mortality.

Keywords: Hip fracture, Neuraxial anaesthesia, General anaesthesia, 30-day mortality, In-hospital mortality, Length of hospital stay

Introduction
The worldwide number of hip fractures in elderly patients will rise due mainly to the demographic change from 1.66 million in the year 1990 to 6.25 million in the year 2050 [1]. Furthermore, elderly hip fracture patients present an array of comorbidities which are associated with an increased risk of morbidity and mortality [2]. The one-month mortality ranges from 4 to 14% [3, 6].
Thus far, the ideal anaesthetic technique (general vs. neuraxial anaesthesia) has not been identified. The most recent randomised studies were condensed in a meta-analysis which was performed in the year 2016. The systematic review of Guy and colleagues included 31 randomised studies published between 1977 and 2013 [7]. However, only 28 studies comprising 2.976 patients could be included for the meta-analysis. Therefore, there is a high bias risk. Obviously the studies have been incapable of addressing, for example, a distinction in the 30-day mortality. Furthermore, there has been a change in clinical practice since 1977 [7]. However, since 2010 several large scale non-randomised studies have been published [8–27]. The objective of the present systematic review and meta-analysis is to provide a six-year overview of the literature assessing the influence of the anaesthetic technique for hip fracture surgery in prospective randomised and retrospective observational studies.

Methods
Protocol and registration
The study protocol has not been previously published. The manuscript has been prepared according to criteria of the PRISMA checklist and guidelines for systematic reviews and meta-analyses [28]. This systematic review and meta-analysis was registered in the international prospective register of systematic reviews (Prospero: CRD42016033254).
Eligibility criteria
Before carrying out the systematic review and meta-analysis the exclusion and inclusion criteria were pre-defined by all authors. We included only human studies, which were published between 01.01.2010 and 21.11.2016 and assessed advantages of the applied anaesthetic technique general vs. neuraxial anaesthesia (epidural or spinal) in adult (≥ 18 years old) hip fracture patients. Prospective randomised and observational studies were included, which addressed the 30-day mortality, in-hospital mortality or length of hospital stay. As secondary outcome we examined the postoperative incidence of myocardial infarction, pneumonia, pulmonary embolism and respiratory failure after hip fracture surgery. We excluded case series and systematic reviews. Studies of all languages were included in the search.
Information sources and search
In March 2017 a systematic search was performed via the database PubMed and Embase. The search term "anesthesia and hip fracture" or "anaesthesia and hip fracture" was used in both databases. Additionally, one study was included which was not identified via the systematic literature search [10]. The full search strategy for PubMed was: (("anaesthesia"[All Fields] OR "anesthesia"[MeSH Terms] OR "anesthesia"[All Fields]) AND ("hip fractures" [MeSH Terms] OR ("hip" [All Fields] AND "fractures" [All Fields]) OR "hip fractures" [All Fields] OR ("hip" [All Fields] AND

"fracture" [All Fields]) OR "hip fracture" [All Fields])) AND ("2010/01/01" [PDat]: "2016/11/21" [PDat]) and for Embase: ((AU = Anesthesia? OR (Anesthesia#)) AND (AU = HIP? OR ((HIP#)) AND (AU = FRACTURE? OR (FRACT####))) AND PY = 2010 to 2016. Additionally, a forward searching in google scholar, a level one reference list searching and a formal searching of trial registries (https://clinicaltrials.gov/; www.who.int/ictrp/en/ (internatio nal clinical trials registry platform) Search Portal of the World Health Organization) was performed. The results of the study of White and colleagues for the hospital length of stay was provided by one of the Co- authors [26].

Study selection and data collection

JVW conducted the literature search and screened all hits based on the full text. Additionally, MC and AS verified all hits for eligibility independently. Only human studies, prospective randomised and retrospective observational studies were included. Case series and systematic reviews were excluded.

Data items

A standardised table based on the PICO approach was made to reveal the salient results [28]. It contains the study type, applied anaesthetic technique, the sample size, primary and secondary outcome variables, summarized results and conclusion. We carried out a meta-analysis for the 30-day mortality, the in-hospital mortality and the length of hospital stay. In addition, we assessed as secondary outcome the postoperative incidence of myocardial infarction, pneumonia, pulmonary embolism and respiratory failure and performed a meta-analysis.

Assessment of risk of bias

In order to assess bias risk, the Cochrane Collaboration's tool for randomised studies was applied. The five domains of bias were classified as high, moderate or low risk. Regarding the non-randomised studies the Cochrane ACROBAT-NRSI tool was used. The seven domains of bias were also classified as high, moderate or low risk, accordingly.

Statistics

The meta-analyses were performed using the RevMan 5.3 software. Due to the clinical and methodological heterogeneity of the included studies a random-effects model was applied for the meta-analysis. *P*-values less than 0.05 were regarded as statistically significant in the seven meta-analyses. The standard deviation (SD) was calculated, if not mentioned, based on the range (Maximum-Minimum)/4 or based on the 95% confidence interval [SD = √N× (upper limit-lower limit)/3.92)] or on the Interquartile Range (IQR) [SD = IQR/1.35], whichever was available.

Results

Study selection

The search in PubMed identified 465 and in Embase 825 studies. The forward searching in google scholar revealed 538 studies, the list one reference searching 662 studies and the formal searching of trials registries 91 studies (clinicaltrials.gov *n* = 71; ICTRP *n* = 20) After removing the duplicates, we screened 1693 studies. Case reports, systematic reviews and meta-analyses were excluded. The study from Helwani and colleagues was included without being identified via our search term ("anesthesia and hip fracture" and "anaesthesia and hip fracture") [10]. Finally 25 full text articles were assessed for eligibility. Two full-text articles were excluded as the outcome parameters did not fit the outcome variables of this study. One study did not define the meaning of the term "local anesthesia", another study described the postoperative length of stay without usable values for our systematic review. The aim of Basques and colleagues was to identify factors, associated with an increased length of stay after hip fracture surgery, like the type of surgery [29, 30]. In total 23 studies were included for this systematic review and meta-analysis, see Fig. Fig.1.1. [8–27, 31–33].

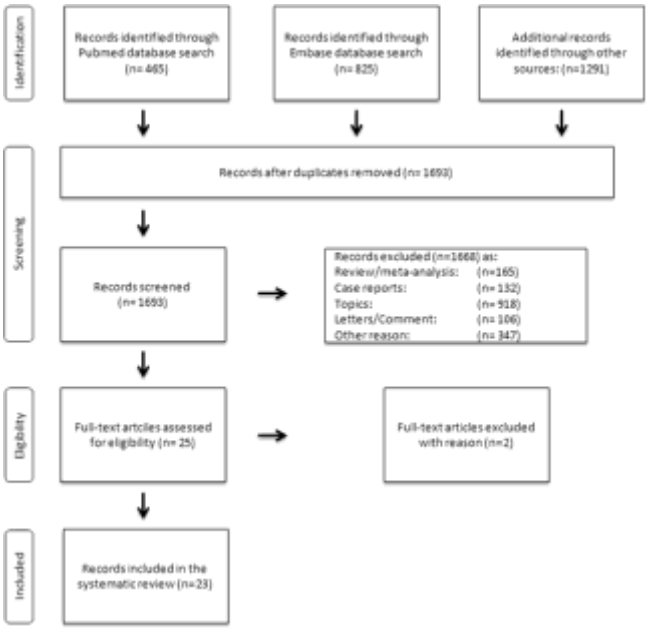
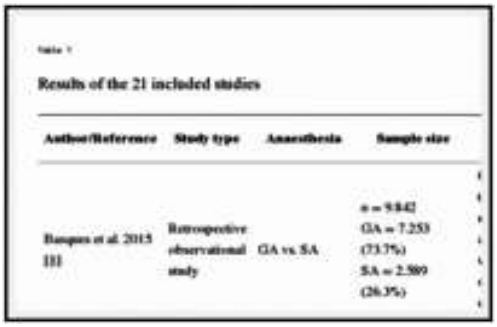


Fig 1: Prisma-flow diagram for the literature search and exclusion criteria

Study characteristics/participants

Twenty retrospective observational studies and three randomised controlled studies were included [8–27, 31–33]. Overall, 413.999 patients were analysed in this systematic review and meta-analysis. 249.408 patients received general anaesthesia and 150.964 patients received neuraxial anaesthesia (spinal anaesthesia and in some cases epidural anaesthesia). Our aim was to include only adult patients with a hip fracture over than 18 years. The study of Rashid and colleagues included patients with an age of 14–98 years. The mean age in the study was 65. Therefore, we decided to include this study in our systematic review [17]. Sample sizes in the included studies varied widely. The largest study included 104.088 patients and the smallest one 45 patients, see Table Table11 [25, 32].



Results of the 21 included studies

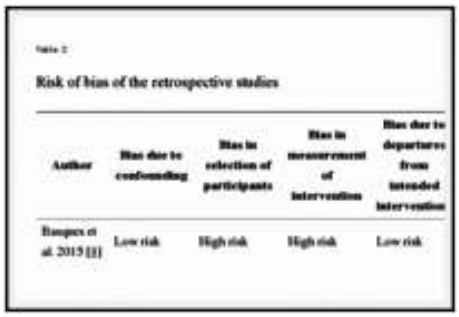
Author/Reference	Study type	Anaesthesia	Sample size
Basques et al. 2015 [8]	Retrospective observational study	GA vs. SA	n = 9.842 GA = 7.253 (73.7%) SA = 2.589 (26.3%)

Table 1: Results of the 21 included studies

Risk of bias within and across studies

Analyses of the risk of bias for retrospective observational

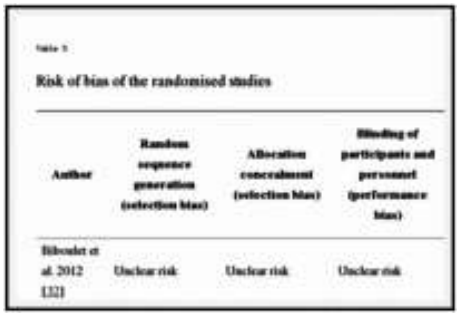
studies and randomised controlled studies are described in Tables Tables22 and and3,3, respectively.



Risk of bias of the retrospective studies

Author	Bias due to confounding	Bias in selection of participants	Bias in measurement of intervention	Bias due to departures from intended intervention
Basques et al. 2015 [11]	Low risk	High risk	High risk	Low risk

Table 2: Risk of bias of the retrospective studies



Risk of bias of the randomised studies

Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)
Biboulet et al. 2012 [32]	Unclear risk	Unclear risk	Unclear risk

Table 3: Risk of bias of the randomised studies

Results of individual studies

Discussion

In our systematic review and meta-analysis we included 23 studies with 413.999 patients. 249.408 patients received general anaesthesia and 150.964 neuraxial anaesthesia (epidural/spinal). We could not detect any difference in the 30-day mortality in patients undergoing hip fracture surgery. However, the length of hospital stay and the in-hospital mortality were significantly shorter in the neuraxial anaesthesia group. Of the secondary outcomes the incidence of myocardial infarction and respiratory failure was significant lower in the neuraxial anaesthesia group. There was no difference in the incidence of pneumonia between the two groups. Of note, out of the 23 studies which met our inclusion criteria, 20 were mainly large retrospective observational studies and three were prospective randomised [8–30]. In 2010 a systematic review carried out by Luger and colleagues examined the type of anaesthesia in hip fracture surgery. They included literature from the years 1967 to 2010 in their systematic review. They were able to include 34 randomised studies, 14 observational studies and 8 systematic reviews and meta-analyses in their study. The authors speculated that spinal anaesthesia may be associated with significantly reduced early mortality, fewer incidents of deep vein thrombosis, less acute postoperative confusion, a tendency to fewer myocardial infarction, fewer cases of pneumonia, fatal pulmonary embolism and postoperative hypoxia [34]. However, the review was limited, as only 18.715 patients were included. With regard to the limited evidence the authors concluded that, neither general, nor regional anaesthesia seem to improve perioperative outcome [34]. To the best of our knowledge, the most recent effort to bundle information in a systematic review addressing the type of anaesthesia in hip fracture surgery has been performed in 2016 by Guay and colleagues in a Cochrane Review. They included only randomised studies from 2003 to 2014. In total 31 studies were included with 3231 patients. Furthermore, only 2152 patients were available to examine the 30-day mortality. They did not find a difference between the two techniques. The authors determined that the number of patients included in the study was insufficient to reveal a difference between general and regional anaesthesia in hip fracture patients [7]. For these reasons we decided to include both prospective randomised and retrospective observational studies to assess as many patients as possible for the systematic review and the meta-analyses. In our systematic review and meta-analysis fourteen studies assessed the 30-day mortality. However, the high number of patients is limited through the high risk of selection bias.

As mentioned above two studies assessed the overall-mortality. Karaman and colleagues revealed that there is a higher mortality rate after receiving general than neuraxial anaesthesia [12]. Shih and colleagues concluded that there is no significant difference between the general and the neuraxial anaesthesia group [18]. Though, there are some limitations. For Karaman and colleagues the overall-mortality was defined as the mortality rate during the length of stay and the follow-up time [12]. Follow-up time was defined as the time period of the study duration. The follow-up time fluctuated between zero and 60 months [12]. For Shih and colleagues overall-mortality means the incidence of death since discharge. Obviously, it is not possible to compare these two overall-mortalities. The neuraxial anaesthesia group of Karaman and colleagues included spinal and epidural anaesthesia [12]. The neuraxial anaesthesia group of Shih and colleagues included only spinal anaesthesia [19].

Five other studies examined the in-hospital mortality [14, 16, 25, 27, 33]. The study of Chu *et al*. revealed a significant higher incidence of in-hospital mortality in the general anaesthesia group [25]. The meta-analysis of the in-hospital mortality showed therefore a significant higher incidence of in-hospital mortality in the general anaesthesia group [14, 16, 25, 27, 33]. The study of Chu *et al*. included 104.088 patients in their study and is weighted in the analysis with 53.2% [25]. The other studies are considerable smaller [14, 16, 27, 33]. The conclusion of the meta-analysis is therefore limited. However, the 30-day mortality rate revealed no difference between the groups. It seems like, if the patient survives the hospital stay, the risk to die in the next weeks is equal whatever anaesthesia technique was applied. Due to aforementioned limitations of the meta-analyses, there is an urge of randomised controlled studies examining the effect of anaesthesia technique regarding the in-hospital and 30-day mortality rates, taking into account possible influencing variables like the age of the patients, pre-existing conditions and type of surgery.

We found a significant shorter length of stay in the neuraxial anaesthesia group compared to the general anaesthesia group. We could include nine studies out of twelve [10, 15, 17, 19, 20, 25, 26, 31, 33]. The other three studies did not mentioned the standard deviation [8, 14, 19]. Due to non-response it was impossible to receive the missing parameters from the authors. Only four studies in the meta-analysis revealed a significant shorter length of stay in the neuraxial anaesthesia group. Three of them are the studies getting the most weight in the analysis [10, 15, 25]. Therefore, our results have to be interpreted with caution. The meta-analysis revealed that the length of hospital stay is one quarter of a day shorter in the neuraxial anaesthesia group, which most likely has no clinical relevance. Another problem is the different

definition of the meaning of length of hospital stay. Most of the authors documented the overall length of stay. In contrast the study of Heidari and colleagues represent the length of stay before and after the surgery [33]. This is an important point, because a delay of surgery extends the length of stay. Helwani and colleagues and Neuman and colleagues showed that neuraxial anaesthesia is associated with a modestly shorter length of stay [10, 15]. In the study of Neuman and colleagues the authors considered the fracture type and the performed surgery procedure [15]. Minimally invasive approaches may decrease the length of stay. Kazemian and colleagues published in 2013 a randomised controlled study examining the treatment of intertrochanteric fractures in elderly patients by a dynamic hip screw and external fixation. The treatment of the hip fracture with the minimal-invasive external fixation showed minimal blood loss, pain reduction, shorter length of hospital stay and favourable functional outcomes compared to the dynamic hip screw [35]. Basques and colleagues revealed that general anaesthesia is associated with a shorter length of stay. However, patients receiving a general anaesthesia were younger, had higher Body Mass Index (BMI) and less comorbidities [8]. The authors used a propensity score to reduce the selection bias and the differences between the two groups, but the length of hospital length of stay was shorter in the general anaesthesia group. The question remains unanswered, if the length of stay in this group was shorter because the patients received general anaesthesia or due to the fact that patients were younger and did not have as many chronic diseases as the older patients who received a spinal anaesthesia. After all the risk of selection bias is high. Another important limitation is the different health care systems of the four included studies for the meta-analysis. The study of Seitz and colleagues and Helwani and colleagues were performed in the United States of America, the study of Sevtap and colleagues in Turkey and the study of Rashid and colleagues in Pakistan [10, 17–20]. Caution is advised when comparing the length of hospital stay of patients with hip fracture in different countries with differing health care systems and discharge points.

In addition we investigated the incidence of myocardial infarction, pneumonia and pulmonary embolism between general and neuraxial anaesthesia after hip fracture surgery. The meta-analysis of the myocardial infarction revealed a significant higher incidence of myocardial infarction in the general anaesthesia group. However, the meta-analysis has got several limitations. All nine studies showed no difference between the two groups. A considerable bias was introduced by the retrospective observational studies. The result of the meta-analysis has to be interpreted with caution.

The meta-analysis of the incidence of postoperative pneumonia indicated no difference between the general and neuraxial anaesthesia groups. Only the study of Shih and colleagues revealed a significant higher incidence of pneumonia in the general anaesthesia group. However the study had only a small sample size of 335 patients [18]. Kamel and colleagues examined 2003 in a study the time to ambulation (walking) after hip fracture surgery. In this study the type of anaesthesia had no influence of the time to ambulation after a hip fracture surgery. However, a prolonged time to ambulation was associated with a longer length of stay and a higher incidence of pneumonia [36].

The meta-analysis of the incidence of the pulmonary embolism showed no significant difference between the general and the neuraxial anaesthesia group. The validity of the meta-analysis regarding pulmonary embolism is limited by the inclusion of only four studies.

Conclusion

In this meta-analysis we could not observe any difference in the 30-day mortality rate between neuraxial and general anaesthesia. Length of hospital stay and the in-hospital mortality was shorter in the neuraxial anaesthesia group. There is an urgent need to carry out large randomised studies, which will reflect “real world” approaches to general and neuraxial anaesthesia, like e.g. the REGAIN trial (www.regaintrial.org.).

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