Background

Blunt Splenic Injuries (BSI) that do not cause haemodynamic compromise are normally managed non-operatively, in an attempt to avoid the morbidity of unnecessary surgery and the risk of Overwhelming Post-Splenectomy Sepsis (OPSS).[1] Multiple studies have attempted to define what factors increase the chances of successful non-operative management (NOM) [2-5] and current Eastern Association for the Surgery of Trauma (EAST) guidelines recommend initial NOM for all haemodynamically normal patients.[6] Despite this, some patients are at predictably higher risk of NOM failure and the challenge is how to identify and manage these patients.[4-7]

Splenic Angio-Embolisation (SAE) for trauma was introduced in the 1980s as an adjunct to NOM, to improve splenic salvage rates.[8,9] High rates of splenic preservation were initially reported [9-11] but subsequent studies have produced conflicting results, with many suggesting no additional benefit.[12-15] Defining which patients would benefit from SAE has been difficult. EAST guidelines recommend considering SAE for patients with American Association for the Surgery of Trauma (AAST) grade III or higher injuries, presence of contrast blush, moderate haemoperitoneum, or evidence of ongoing bleeding.[6]

With the lack of clear indications for SAE, approaches to its use have varied, ranging from conservative use to relatively unselective liberal use.[11,15,16] A potential disadvantage of a liberal approach is that some patients may be exposed to unnecessary intervention, and SAE is associated with a degree of risk. Major complications occur in 14% to 29 % of patients.[16-18]

SAE use is increasingly common in trauma centres, but the evidence supporting this practice is predominantly from retrospective uncontrolled studies.[6] A 2011 systematic review

concluded that SAE significantly decreased failure rates in grade IV and V injuries, but was limited in that it compared NOM failure rates in a population drawn from one group of studies, with SAE failure rates from different studies. Only US studies were included.[19] Another meta-analysis compared cohorts before and after the introduction of SAE, but did not directly compare patients who underwent SAE to those who did not.[7] Several studies have been published since, including a larger prospective multi-centre study.[20] But there has been no further systematic analysis comparing outcomes following the two treatment options. The aim of this systematic review is to compare the safety and effectiveness of SAE as an adjunct to non-operative management versus non-operative management alone (NOM) in adults with blunt splenic injury.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Meta-Analyses (PRISMA) guidelines [21] and was prospectively registered with the PROSPERO database, ID number CRD42016035616.[22]

Search strategy

Relevant publications were identified by an electronic search of the Medline, Embase and CINAHL databases using combinations of the following keywords and medical subject headings (MeSH) terms: 'trauma', 'wounds and injuries', 'diseases, splenic', 'spleen', 'splenic', 'artery, splenic', 'embolization, therapeutic', 'embolisation' and 'angio-embolisation'. The full Medline search strategy is available in the Supplemental Evidence (eFigure 1). Searches were limited to English-language and human studies. The last search was performed on 1st May 2016. Two authors independently screened the search output for potentially relevant citations, and then assessed the full text of all identified citations for eligibility. Divergence was resolved by consensus with a third independent reviewer. The reference lists of relevant articles were searched to identify additional publications.

Eligibility Criteria

Randomised trials and non-randomised observational studies that reported data on our primary or secondary outcomes were eligible for inclusion. Participants needed to be adults (>16 years) admitted to hospital with blunt splenic trauma, not undergoing immediate splenectomy. The intervention was SAE (as an adjunct to non-operative management) and the comparison was non-operative management alone. Studies were excluded if they: did not clearly report the population, treatment, or outcomes of interest; or considered only paediatric

injuries. Where two or more studies were published using the same or overlapping cohorts, the most recent, or larger, cohort was included.

Quality and Risk of Bias assessment

Methodological quality was assessed at study-level using the Newcastle-Ottawa Scale [23], and at outcome-level using the GRADE framework.[24] Publication bias was assessed visually with a funnel plot.

Outcome data and definitions

The primary outcome was failure of non-operative management. Secondary outcomes included morbidity, mortality, transfusion requirements, and hospital length of stay. NOM was defined as close observation, including blood transfusion, but excluding angiography, embolisation, or surgery. SAE was defined as non-operative management with adjunctive splenic angioembolisation. Failure was defined according to the definition used in the primary study.

Data extraction

Two investigators independently extracted methodology, population, treatment, and outcome data using a standardised proforma. Discrepancies were resolved by consensus. The following data were extracted from each study: study design, population, eligibility criteria, sample size, SAE indications, definition of failure, splenic injury grade, treatment delivered, splenic salvage rate, morbidity, mortality, transfusion requirements, and hospital length of stay.

Statistical analysis

Meta-analyses were performed with JAGS software using a Bayesian method.[25] A Bayesian approach to meta-analysis offers a number of advantages over traditional frequentist approaches.[26] These advantages are particularly valuable in a meta-analysis of observational studies where heterogeneity, small sample sizes, non-normal data distribution, and zero event rates are expected. A Bayesian approach is able to address these difficulties directly.[26,27] The Bayesian network used in this study explicitly models between-study heterogeneity and within-study variability, does not assume normal data distribution, and does not require the addition of a continuity factor for analyses when the event rate is zero. In addition, the Bayesian approach allows the calculation of a 95% Credible Interval (CrI) and the ability to perform hypothesis tests using the entire posterior distribution of the parameter estimate. Hypothesis tests that use posterior probabilities address the clinical question more directly than traditional significance tests using a null hypothesis.[28]

An absolute (Risk Difference, RD) and relative (Risk Ratio, RR) measure of treatment effect, together with their corresponding 95% Credible Intervals (CrI), were calculated for dichotomous outcomes in individual studies. Mean Difference (MD) with 95% CrI was calculated for ordinal outcomes. Measures of treatment effect were pooled using a Bayesian random-effects model (Supplemental Evidence).[27] A pre-specified subgroup analysis, stratifying patients by AAST splenic injury grade, was performed for the primary outcome, and treatment effect reported as RD with 95% CrI. Heterogeneity was reported as the I^2 statistic. For meta-analyses of RRs, the posterior probability (P) that the pooled estimate is less than 1, and for meta-analyses of RD and MD, the P that the pooled estimate is less than 0, were calculated. $P > 0.95$ is considered strong evidence of a beneficial effect of SAE over NOM alone.

Results

Search

The search identified 1134 unique citations, of which 160 were potentially relevant. Overall, 23 studies were included [figure 1]. Sixty-six studies were excluded because of an ineligible study population: no direct comparison of SAE and NOM (55), paediatric only (8), animal (2), and non-trauma (1). Fifty-nine studies had an ineligible study design: review (25), case report (15), abstract (11), survey (1), or letter to the editor (7). Five studies did not report outcomes adequately, and four were not published in English. Three studies used the same dataset as others so only the most recent version of the dataset was included.[29-31] Clinical and methodological characteristics of the included studies are presented in Tables 1 and 2.

Methodological quality and risk of bias

No randomised controlled trials were identified. Three prospective- and 20 retrospective cohort studies were included.[13,15,20,32-51] Mean Newcastle-Ottawa Score was 6.9 (range 6-8). There were important differences between study populations, including differences in the grade of splenic injury and overall injury severity (Table 2). This explains some of the heterogeneity between studies. There was no evidence of publication bias. Follow-up was complete to hospital discharge in the majority of studies. Due to high risk of bias and confounding factors, all studies were considered of low methodological quality by GRADE guidelines.

Indications for SAE

Indications for SAE varied. Specific indications included splenic injury grade 3 or higher,[33,36,40,45] grade 4-5,[15,34,41,44,48,50] contrast blush[15,20,34,39,40,44,48,50] or evidence of

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vascular injury on CT scan,[20,36,41,45,48,51] evidence of ongoing bleeding,[15,34,35,36,39,42,44,51] large haemoperitoneum,[15,41,44,48] and/or clinician's discretion.[13,33,40,41,45] No explicit indication was stated in seven studies.[32,37,38,43,47] Studies frequently cited more than one indication, and clinician discretion was often the overriding factor.

Definition of failure

Definitions of failure also varied. Fifteen papers defined it as progression to splenectomy,[15,20,32-35,39,41,42,44-46,49,50] three as evidence of ongoing bleeding,[13,37,43] three as requirement for further procedure,[46,48,51] and two provided no definition.[36,38]

Failure Rates

Twenty-two studies, describing 6415 patients with BSI, directly compared failure rates for those treated with SAE and those treated with NOM alone.[13,15,20,32-37,39-51] There was high heterogeneity between studies (I^2 = 59.5%). The overall failure rate, for all injury grades combined, was similar following both treatments (SAE, 88/1027 [8.6%] *versus* NOM, 416/5388 [7.7%]; RR 1.09 [0.80 to 1.51]; P (RR<1) = 0.28) (Figure 2 and eFigure 2). The average duration from injury to failure of non-operative management was 2.7 (range 0 – 25) days.

When stratified by injury grade, there was no significant difference in the risk of treatment failure following SAE or NOM for grade I, II, or III splenic injuries. However, patients with grade IV or V splenic injuries had significantly lower failure rates when treated with SAE, compared to those treated with NOM alone (Figures 3 and 4).

Morbidity

Three studies, describing 333 patients with BSI, reported overall morbidity rates.[37,38,41] Heterogeneity between these studies was minimal (I^2 = 10.4%). Morbidity was significantly higher in patients treated with SAE compared to those treated with NOM alone (SAE, 43/113 [38.1%] *versus* NOM, 41/220 [18.6%]; RR 1.83 [1.20 – 2.66]; P (RR<1) < 0.01). Twelve studies reported complications after SAE, including splenic abscess, infarction, pseudocyst or vascular injury, pancreatitis, intestinal perforation, abdominal compartment syndrome, acute respiratory distress syndrome and multi-organ failure.[15,33,36,37,38,41,44,45,47,49]

Mortality

Seven studies, describing 2060 patients with BSI, compared mortality rates for those treated with SAE and those treated with NOM alone.[13,15,32,38,40,43,45] Heterogeneity between these studies was minimal (I^2 = 1.7%). Mortality rates following both treatments were similar (SAE, 18/375 [4.8%] *versus* NOM, 97/1685 [5.8%]; RR 0.82 [0.45 – 1.31]; P (RR<1) = 0.81).

Hospital Length of Stay

Three studies, describing 992 patients with BSI, reported the average duration of hospital admission.[15,38,43] There was substantial heterogeneity between studies (I^2 = 68.5%). Patients managed with SAE had a similar hospital length of stay to those managed with NOM alone (11.3 *versus* 9.5 days, MD 1.74 [-0.61 to 5.06]; P (MD<0) = 0.06).

Blood transfusion

Two studies, describing 107 patients with BSI, reported blood transfusion requirements.[33,46] There was no significant difference in the mean volume of blood transfused to patients treated with SAE compared to those treated with NOM alone (1.8 *versus* 1.7 units, MD 0.08 [-2.44 – 2.88]; P (MD<0) = 0.47)

Discussion

This study provides the first comprehensive meta-analysis of outcomes following non-operative management (NOM) of blunt splenic injury, allowing a direct comparison between those managed with and without splenic angio-embolisation (SAE). Overall, for Grades I – V combined, there was no difference in NOM failure rates, mortality, hospital length of stay, or blood transfusion requirements, between patients treated with SAE and those treated with NOM alone. However, morbidity was significantly higher in patients treated with SAE. When stratified by grade of splenic injury, SAE significantly reduced the failure rate of NOM in patients with grade IV and V splenic injuries, but had minimal effect in those with grade I to III injuries.

Our findings are consistent with a previous meta-analysis. Requarth *et al* described an overall NOM failure rate of 15.7% when SAE was used as an adjunct and 17.4% for observation alone, compared to our findings of 8.6% and 7.7% respectively. They concluded that SAE significantly reduced the failure rate of NOM for grade IV and V splenic injuries. An important limitation of this study, however, is that they compared the outcomes of patients undergoing SAE described in one set of studies, with the outcomes of conservatively managed patients from a different set of studies. [19]

Multiple studies have described the introduction of SAE and concluded that SAE significantly reduces the failure rate of non-operative management.[52-55] Many of these studies were included in a recent systematic review that reached the same conclusions.[7] The results of these studies are at high risk of bias, as they compare contemporary with historical cohorts. Notwithstanding general improvements in

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trauma care between cohorts, the management of blunt splenic injury, including the indications for non-operative management, has changed significantly over time. [56] In addition, the ability to detect lower grade injuries, with a lower risk of NOM failure, has improved.[13]

A number of predictors for failure of NOM have been suggested.[4] These include patient age, haematocrit, haemodynamic status, Glasgow Coma Score, Injury Severity Score (ISS), AAST grade, and degree of haemoperitoneum. It is widely accepted that haemodynamically unstable patients should undergo laparotomy,[57] thus leaving severity-of-injury metrics as the most discriminating predictors of failure. Most BSI studies have used evidence of ongoing haemorrhage and AAST splenic injury grade to determine the need for SAE, using either grade III or grade IV injury as a threshold. Our results support guidance to consider SAE as an adjunct to non-operative management of grade IV and V splenic injuries [6,56], but do not support its role in grade III injuries.

In many studies, patients were embolised for clinical or radiographical evidence of ongoing bleeding, which NOM patients lacked. This finding was defined variably, such as moderate or large haemoperitoneum or contrast blush, and was inconsistently utilised as an indication for SAE across the studies. Some studies use splenic vascular injury, such as pseudoaneurysm or arteriovenous fistula, as an indication for SAE.[20,36,45,48,51] The reporting of this information was inconsistent, and we were unable to extract sufficient data to allow a subgroup analysis and determine the effect of these factors on failure rates. Post et al note no differences in hospital stay, mortality nor need for further procedures between patients with contrast blush who

were observed versus those undergoing embolisation.[46] Zarzaur et al found no difference in outcomes for patients with contrast blush who were embolised, versus those who were not.[20]

CB has also been shown to be a predictor of NOM failure.[58,59] Although it is often assumed that it is this group of patients who benefit most from SAE, Tugnoli *et al* note that absence of CB in high-grade injuries does not reliably exclude bleeding and postulate that this may account for high reported failure rates of NOM for high-grade injuries, as SAE is rarely performed without evidence of CB. They conclude that all grade 4-5 injuries should be embolised. Others have found that addition of SAE does not improve failure rates for these injuries, and recommend against it.[13,15] There is little good quality data to support either approach, and our study cannot answer this important question, as no paper specified which patients had CB. Nor is there a method for determining the degree of CB that is clinically significant.[57] Active intraperitoneal bleeding and arteriovenous fistulae are also felt to have a high risk of failure even with embolisation.[60,61]

It is important to define which patients are likely to benefit from SAE, as it is not a risk-free intervention. Complications were reported variably; some papers reported no complications at all [34,35] while others describe serious complications.[33,36,37,40,41,49] Duchesne *et al* found a four-fold increased risk of Acute Respiratory Distress Syndrome (ARDS) with SAE use when compared to splenectomy.[12] Our meta-analysis found a substantial increase in overall morbidity with SAE, though the higher injury severity in the SAE cohort confounds this finding. It is still not known whether splenic immune function is preserved after SAE [62,63] or whether it simply avoids

operative splenectomy. [12] When considering whether to utilise SAE as an adjunct to NOM, clinicians must consider the risks and benefits. SAE is not an operation and so remains a component of non-operative management, but it is more invasive than no intervention at all. Our findings suggest that for grade IV and V injuries, the benefits of SAE outweigh the risks of serious complication. For lower grade injuries, the chance of complications and minimal evidence of additional benefit make its use unwarranted.

This study has a number of limitations. First, many included studies have small sample sizes, heterogeneous populations, and use variable indications for SAE. There were frequently differences between cohorts for which there was no adjustment or control. Most obvious is the difference in AAST grade, and this review has made some attempt to control for this by subgroup analysis by grade, but other differences such as ISS, CB, and vascular injury are not reported and may confound the results. Second, there was variability in the definition of NOM failure. The majority of studies regard this as progression to splenectomy, but in some it was evidence of ongoing bleeding (not further defined). Mortality and transfusion requirement may limited by equilibration bias. Those patients with an early major transfusion requirement are likely to have proceeded directly to splenectomy and thus differences between the cohorts may be minimal. Our findings should be considered in this light. Uncertainties merit clarification in the form of further studies to investigate the role of these factors, to better define indications for SAE. A 2011 survey of AAST members suggested there is enthusiasm to conduct these studies.[64]

Conclusion

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SAE significantly improved the success of non-operative management of AAST grade IV and V blunt splenic injuries, but had no demonstrable benefit for grade I, II, and III injuries. Overall, SAE increased the morbidity associated with non-operative management, but was not associated with any improvements in mortality, hospital length of stay, or transfusion requirements, when compared to patients treated with non-operative management alone.

Author Contribution

JC: Original concept, protocol design, data search and extraction, data synthesis and interpretation, write-up

KN: Secondary reviewer and data extraction, critically reviewed manuscript

BY: Statistical analysis and production of figures

ZP: Original concept, protocol design, data interpretation, write-up

SB: Senior author, contributed to study design, data interpretation and critical revision of the manuscript

All authors read and approved the final manuscript

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Figure Legends

Figure 1: PRISMA flow chart of study selection process

Table 1: Clinical characteristics of included studies

Table 2: Methodological characteristics of included studies

Figure 2: Forest plot of the relative risk (Risk Ratio) of failure of non-operative management of blunt splenic injury. SAE, non-operative management with adjunctive splenic angio-embolisation; NOM, standard non-operative management.

Figure 3: Absolute risk (Pooled Risk Difference) of failure of non-operative management of blunt splenic injury, stratified by American Association for the Surgery of Trauma (AAST) grade of splenic injury. SAE, non-operative management with adjunctive splenic angio-embolisation; NOM, standard non-operative management. *Posterior probability that the pooled risk difference estimate is less than zero.

Figure 4: Failure rate of non-operative management of blunt splenic injury, stratified by American Association for the Surgery of Trauma (AAST) grade of splenic injury. SAE, non-operative management with adjunctive splenic angio-embolisation; NOM, standard non-operative management. Failure rate presented as percentage with 95% Credible Interval.

Supplemental evidence

Bayesian random effects model

eFigure 1: Funnel plot of effect size against sample size for 22 included studies describing failure rate of non-operative management of blunt splenic injury.

eFigure 2: Meta-analysis of the absolute risk difference in failure of non-operative management of blunt splenic injury. SAE, non-operative management with adjunctive splenic angio-embolisation; NOM, standard non-operative management.

eFigure 3: Example Medline search strategy