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REVIEW

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Comparative evaluation of efficacy and safety of automated versus manual red cell exchange in sickle cell disease: A systematic review and meta-analysis

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Abstract

Background and Objectives: Exchange transfusion is a valuable treatment option in sickle cell disease (SCD) and is preferred over simple transfusion as it removes abnormal haemoglobin S (HbS) levels and reduces complications. This meta-analysis aims to evaluate the efficacy and safety profile of automated red cell exchange (aRBX) procedure over manual red cell exchange transfusion (MET) in SCD patients.

Materials and Methods: A standard meta-analysis protocol was developed, and after performing a comprehensive literature search in PubMed/MEDLINE, Cochrane and International Clinical Trial Registry Platform (ICTRP), reviewers assessed eligibility and extracted data from nine relevant studies. A random effects model was used to estimate the pooled effect size calculated from the mean difference in HbS percentage, serum ferritin level and risk ratio for the adverse events. Quality assessment was done using the risk-of-bias assessment tool, and a summary of observations was prepared using standard Cochrane methodology with GradePro GDT.

Results: The random-model analysis revealed a mean difference of 4.10 (95% CI: −3.29–11.49; $Z = 1.09$; $p = 0.28$) for HbS percentage, mean difference of 435.29 (95% CI: −73.74–944.32; $Z = 1.68$; $p = 0.09$) for serum ferritin and pooled risk ratio of 1.35 (95% CI: 0.63–2.87; $Z = 0.77$; $p = 0.44$) for adverse events.

Conclusion: This meta-analysis did not reveal any significant benefit of aRBX in reducing HbS percentage and attenuating the serum ferritin level when compared with MET. There was also no significant increased risk of adverse events detected in association with aRBX.

KEYWORDS
apheresis: therapeutic, patient blood management, transfusion reactions, transfusion strategy: red cell components, transfusion therapy

Highlights

- Sickle cell disease (SCD) is a haematological disorder with autosomal recessive inheritance.
- Exchange transfusion is a life-saving treatment modality in vaso-occlusive crisis due to SCD.
- The efficacy and safety profile of automated versus manual exchange procedures have been hardly recognized in the literature.

INTRODUCTION

Sickle cell disease (SCD) is one of the most common inherited genetic disorders caused by a single point mutation of the β-globin gene that produces haemoglobin S (HbS) [1]. This abnormal HbS leads to many acute complications such as stroke, acute chest syndrome (ACS), vaso-occlusive crisis (VOC), splenic sequestration and severe infection. Patients with SCD also have some chronic complications such as pulmonary hypertension, retinopathy, nephropathy and sometimes osteonecrosis [1, 2].

Presently, three major therapeutic modalities are available: blood transfusion, administration of hydroxyurea and bone marrow transplantation [3]. Although hydroxyurea has shown clinically proven efficacy with significant improvement of VOC and ACS, many breakthrough trials have shown that chronic transfusion therapy can prevent stroke, reducing the frequency of vaso-occlusive pain crisis and acute chest syndrome–related hospitalizations as well as other chronic complications related to SCD [4–6]. Blood transfusion in SCD mainly aims to correct anaemia and improve the oxygen-carrying capacity, as transfusion of normal red blood cells (RBCs) carrying normal haemoglobin A (HbA) dilutes the circulating level of sickled HbS, thus diminishing impaired erythropoiesis, haemolysis and vaso-occlusive events, which are major contributors to the complications of SCD [7, 8].

There are three different modalities of RBC transfusion in SCD: simple transfusion (ST), manual exchange transfusion (MET) and automated red cell exchange (aRBX) transfusion, also termed erythrocytapheresis [9]. In exchange transfusion, the sickled RBCs in SCD are removed and replaced with normal donor RBCs. Exchange transfusion is preferred over ST, as it maintains the HbS level within target ranges or even rapidly decreases the level of HbS, prevents iron overload and volume overload, and also minimizes the rise in blood viscosity [8, 10]. In MET, whole blood is phlebotomized immediately before transfusion, and the net iron load is reduced by more than 15% when compared to ST. MET is advocated if there is a lack of high-flow venous access, patients have low body weight (less than 25 kg) and the setting is resource-constrained [7]. However, unlike MET, aRBX requires specialized equipment called apheresis, as well as expertise. Automated exchange is a faster procedure with continuous fluid balance but requires good venous access and the use of anticoagulation. In aRBX, the net iron load can be reduced further by modulating the post-exchange target haematocrit (Hct) [9, 11, 12]. It also increases RBC exposure, as the number of RBCs needed for each procedure is higher than in MET and possibly increases the risk of alloimmunization [10].

Presently, evidence from observational studies and clinical trials exploring the efficacy of aRBX over MET in attenuating the post-exchange sickled HbS as well as reducing the iron overload is limited. Moreover, the safety profile of aRBX over MET is also contradictory [8, 10, 13]. Hence, it is important to generate evidence regarding the magnitude of the efficacy and safety of aRBX in SCD patients for framing therapeutic guidelines on red cell exchange procedures. So, the present meta-analysis has been planned to evaluate the efficacy, safety and tolerability profile of aRBX as one of the treatment modalities in SCD.

MATERIALS AND METHODS

Development and registration of protocol

A standard meta-analysis protocol for systematic reviews and meta-analysis was registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO Registration Number: CRD42021268069) [14–16]. The protocol of the meta-analysis was exempted from full review and approved by the Institutional Ethics Committee, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, as per the Indian Council of Medical Research (ICMR) 2017 guideline, on 21 April 2018.

Literature search

A systematic literature search was performed independently by four review authors (S.M., A.S., S.P. and G.K.R.) using PubMed/MEDLINE, Cochrane and the WHO International Clinical Trials Registry Platform (ICTRP) databases for prospective clinical trials and observational studies on the efficacy and safety of aRBX procedure in reducing HbS percentage and attenuation of iron overload in terms of serum ferritin in comparison to MET procedure till May 2021. Only studies published in English language were included for the meta-analysis; however, the search strategy was not restricted by the date of publication. PICO scheme was followed for reporting the inclusion criteria. Key elements that we used in our search using MESH terms were the 'P' (anaemia, sickle cell/sickle cell disease/disease, haemoglobin S/cell disorder, sickle/HBS disease); the 'I' (Exchange transfusion, whole blood/Cytapheresis, Instrumentation/Cytapheresis, methods/Erythrocyte transfusion, methods/Erythrocyte transfusion, therapy/Erythrocyte transfusion, automation); the 'C' (Manual exchange, Erythrocyte transfusion/Erythrocyte transfusion/whole blood/Exchange transfusion, whole blood) and the 'O' (Efficacy/percentage decrease in Sickled Haemoglobin [HBS]/decrease in serum ferritin/tolerability and safety profile in terms of any complications or adverse events associated with aRBX procedure [e.g., hypocalcemia, hypotension, vasovagal attack]), and complications related to venous access (e.g., catheter flow obstruction, venous port infection, or thrombosis), alloimmunization, or any other technical concerns.

Study selection criteria

Types of studies

Prospective clinical trials and observational studies that evaluated the effect of red cell exchange in decreasing the HbS percentage in SCD as a primary outcome were included in this meta-analysis. Review articles, letters to the editor, comments, case series, case reports and

studies in which it was impossible to retrieve or calculate data of interest were excluded from this review.

Types of participants

Both paediatric and adult patients of the age group range 4–66 years of both sexes with a history of acute SCD complications such as stroke, ACS and VOC; history of chronic SCD complications such as primary and secondary stroke; recurrent acute complications such as VOC, ACS, or priapism, fulfilling as criteria for indication of chronic RBC exchange transfusion in preventing these episodes as per the American Society for Apheresis (ASFA) guideline were included in this review [17]. SCD patients who required exchange transfusion as a pre-operative measure of a major surgery to reduce the HbS percentage were also included in the study.

The exclusion criteria included SCD patients who were only on an ST regime and not indicated for red cell exchange transfusion as per the ASFA guideline.

Types of interventions

Experimental intervention: aRBX procedure performed on SCD patients in different clinical conditions as indicated by the ASFA guideline.

Control intervention: MET performed on SCD patients as per the same indication mentioned in the ASFA guideline.

Types of outcome measures

1. Primary outcome
   a. Change in the percentage of reduction of HBS
2. Secondary outcomes
   a. Change in serum ferritin level
   b. Complications related to the procedure, especially during aRBX such as vasovagal syncope/attack, hypocalcaemia, hypotension and hypothermia and catheter-related adverse events
3. Rate of RBC alloimmunization

Data extraction and management

We contacted authors of the studies to resolve any uncertainties and asked for additional unpublished data for this meta-analysis. Extracted data included the following:

1. Publication type and source
2. Trial design including timing, follow-up, sequence generation and allocation concealment
3. Setting, including the country, and the level of care
4. Participants satisfying the selection criteria and number of dropouts
5. Interventions including the number of procedures/sessions performed for each type of red cell exchange (i.e., MET vs. aRBX), time between the procedures, route of administration and duration of treatment
6. Outcome measures as specified above

Data analysis

This meta-analysis was conducted using the Cochrane Program Review Manager Version 5.3 and the 'meta' package of R programming (Version 4.1.0) [18].

The mean difference and risk ratio were calculated to estimate the effect size for continuous and categorical variables, respectively. The random effects model was used for between-group analyses, irrespective of heterogeneity between individual sample sizes. The outcome was depicted as a point estimate with 95% confidence interval. Chi-squared test was used to assess whether the observed differences in results were compatible with chance alone. I^2 statistics, which describes the percentage of the variability in effect that is due to heterogeneity, was performed for quantifying inconsistency.

In case of significant heterogeneity, the result was further investigated by performing sensitivity analysis to test the robustness of the results obtained in the present meta-analysis. We also performed a subgroup analysis between the studies, as the effect size may be potentially modified because of inclusion of both observational studies and clinical trials. We constructed funnel plots and performed Egger regression test and Begg and Mazumdar rank correlation as a quantitative test for publication bias. Standard Cochrane methodology and the GRADE Working Group guidance were followed to create a 'Summary of findings' table, and five grade considerations (risk of bias, consistency, imprecision, indirectness and publication bias) of the included methods and results of the included studies were considered to conclude the certainty of the evidence for each outcome [19]. We described the risk of bias for observational studies and for randomized controlled trials and judged them as low moderate, serious, critical and low, some concerns and high.

RESULTS

Description of included studies

The database searches identified 483 publications, which were reduced to 460 after duplicates were removed. These publications were screened by title and abstract for eligibility, and 444 studies were excluded from the study. The reasons for exclusion were as follows: review articles, case reports, letters to the editor, practice guidelines, literature in Spanish, French, German and Dutch, and studies unrelated to the subject of the present meta-analysis. The results of the searching and screening process are shown in the PRISMA flow chart (Figure 1). After screening, 16 studies were retrieved for full-text assessment. Finally, nine full-text articles were included in the meta-

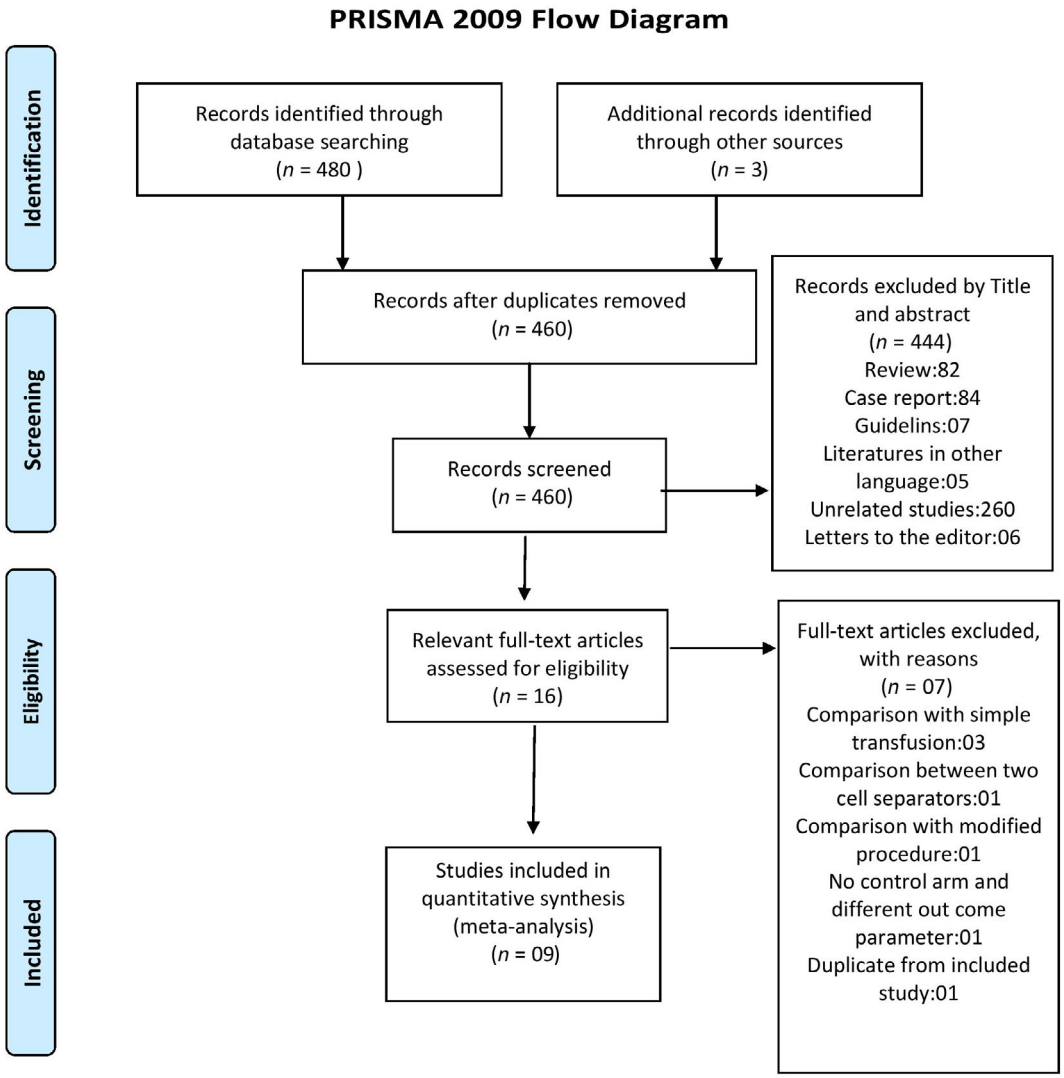

FIGURE 1 Study identification and selection process as per PRISMA guideline

analysis [3, 7–10, 13, 20–22]. Out of these included studies, eight studies were either prospective or retrospective observational studies [3, 7–10, 13, 21, 22] and one study was a randomized controlled trial [20]. The details of the included studies are described in Table S1. The remaining seven full-text articles [23–29] were excluded; three of them [23, 28, 29] compared aRBX with ST; one study [26] compared the effect of aRBX in SCD with two different cell separators (Spectra OPTIA vs. COBE Spectra); another study [27] compared conventional RBC exchange with the modified procedure of isovolumic haemodilution; another one [25] had no control arm as a comparator and a different outcome parameter; and one study [24] was duplicate of an already included study (Table S2). Assessment of the risk of bias of all included studies was separately performed for data of randomized controlled trials and observational studies with the help of the R programming in the 'robvis' package, that is, ROB2 and ROBINS-I, respectively. The risk-of-bias plot was produced by the 'robvis' package via the 'rob_traffic_light' function for better understanding, and is shown in Figure 2a,b.

Effect of intervention

The effect of aRBX compared with MET in SCD patients on the reduction of HbS level, decrease of serum ferritin level, and other complications associated with the procedures, such as catheter-related complications, vasovagal attack, hypotension, hypocalcaemia and any other complications observed in the included literature, was evaluated in this meta-analysis. The effect sizes of the included studies were compared using the Cochrane Program Review Manager, version 5.4 using a random effects model.

HBS level

Six studies [7, 8, 10, 13, 20, 22] from the included literature described the primary outcome, that is, change in the reduction of HbS percentage. The mean and standard deviation from median and inter-quartile range were determined with the on-line calculator

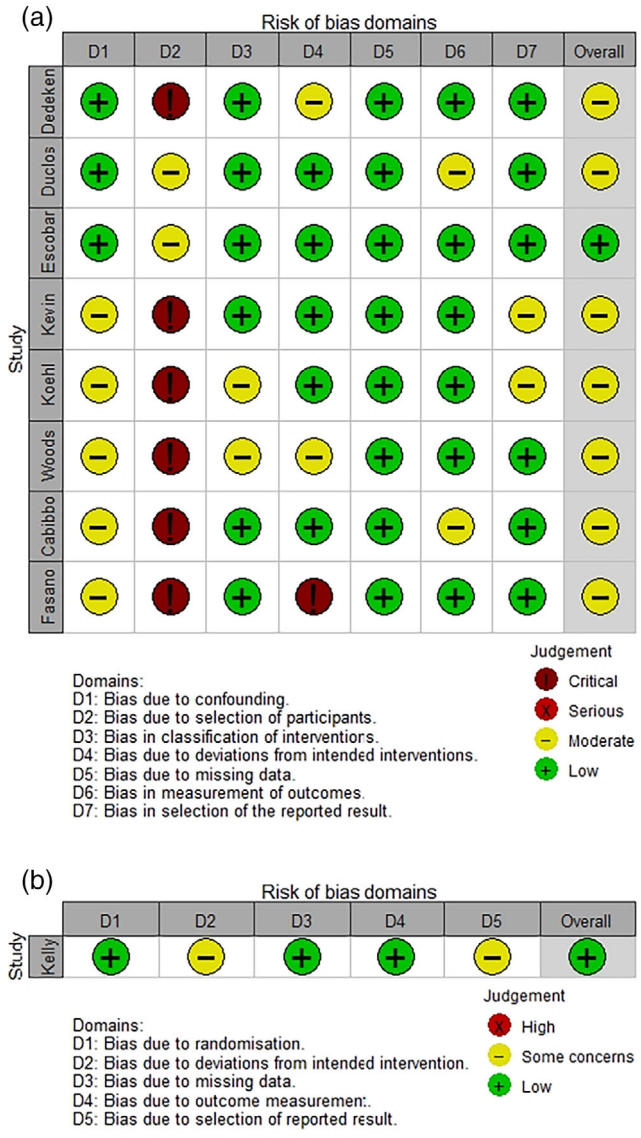

FIGURE 2 Risk-of-bias graph: (a) observational study, (b) clinical trial

formulated and described by Luo and Wan et al. [30, 31]. The test of heterogeneity was 45% and the *p*-value was not significant. The random model analysis of the studies did not find any significant reduction of the HbS value in the aRBX group (Figure 3a). Despite low heterogeneity, we excluded the study by Kelly et al. [20], as their study included data retrospectively from a randomized trial [20]. We observed a significant mean difference of HbS of 5.72 (95% CI: 0.48–10.95; $Z = 2.14$; $p = 0.03$), favouring the higher reduction of HbS percentage in the aRBX group (Figure 3b). Moreover, the heterogeneity of the studies was also reduced considerably to 11%. The study by Escobar et al. [8] had shown a significant reduction of HbS percentage in the aRBX arm. After excluding this study, the heterogeneity had dropped significantly to 9%, but, overall, the effect size remained non-significant (Figure 3c). Subgroup analysis comparing observational study with the clinical trial to detect the impact of clinical trial over observational study was also significant, as shown in Figure 3d.

Serum ferritin level

Six studies from the included records described the change in serum ferritin level [3, 7, 9, 10, 20, 21]. The test of heterogeneity was significant (heterogeneity: $\chi^2 = 75.91$, $df = 5$ [$p < 0.00001$]; $I^2 = 93\%$; $n = 175$). The random effects model analysis of these studies indicated a trend of serum ferritin reduction towards the aRBX group as compared to those treated with MET despite no statistical significance in the pooled effect size (Figure 4a). Sensitivity analysis was performed in view of significant heterogeneity. The heterogeneity was nullified, and the pooled mean difference became significant after removing the study by Kelly et al. [20], indicating a significant reduction of serum ferritin in the aRBX group (Figure 4b). The heterogeneity and the pooled effect size were not significant following exclusion of the other studies. Further, subgroup analysis by comparing the observational studies with the clinical trial by Kelly et al. [20] was significant (Figure 4c).

Adverse events

We included seven studies from the records and calculated the risk ratio of the adverse events in our meta-analysis [3, 7, 8, 10, 13, 21, 22]. The test of heterogeneity was not significant and random effects model analysis revealed a pooled risk ratio of 1.35 (95% CI: 0.63–2.87; $Z = 0.77$; $p = 0.44$), indicating that adverse events were not significantly associated with aRBX. We did not perform sensitivity analysis because there was no significant heterogeneity observed among the studies (Figure 5a).

Procedure-related adverse events

We analysed the adverse events that were specifically related to the red cell exchange procedure, and the test of heterogeneity showed its almost absence (heterogeneity: $\chi^2 = 5.13$, $df = 5$ ($p = 0.40$); $I^2 = 3\%$; $n = 33$). The pooled risk ratio of this random analysis was 2.27 (95% CI: 0.99–5.19; $Z = 1.94$; $p = 0.05$), showing a trend towards aRBX, as we observed a higher number of procedural complications with aRBX (Figure 5b). Although the heterogeneity among the studies was very small, we still performed sensitivity analysis after excluding the study by Escobar et al. [8], as this study did not mention any procedural complications with aRBX. We noted nil heterogeneity (heterogeneity: $\chi^2 = 1.83$, $df = 4$ ($p = 0.77$); $I^2 = 0\%$; $n = 29$) following sensitivity analysis and with the significant pooled risk ratio of 2.8 (95% CI: 1.22–6.51; $Z = 2.42$; $p = 0.02$), indicating that a significantly high number of procedure-related adverse events are encountered with aRBX compared to MET (Figure 5c).

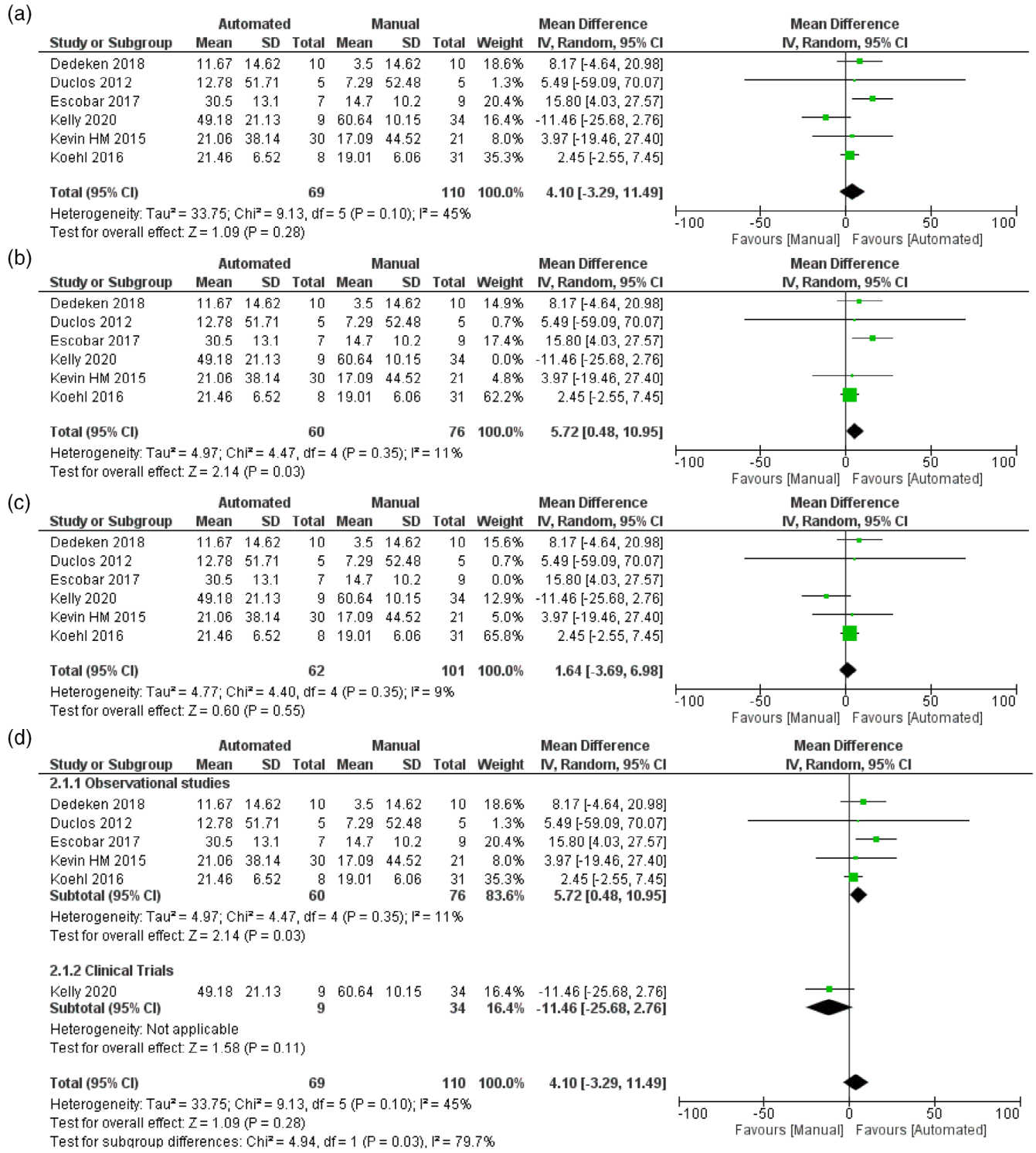

FIGURE 3 Forest plot illustrating the mean difference of change in HbS level in automated versus manual red cell exchange procedure (a), after sensitivity analysis excluding Kelly et al. (b), after sensitivity analysis excluding Escobar et al. (c), and subgroup analysis for observational studies and clinical trial (d)

Catheter-related adverse events

We separately analysed catheter-related adverse events, especially infection, blockage, or thrombosis, due to the intervention with aRBX or MET. We identified only three studies that described catheter- or venous access-related complications [8, 21, 22]. Out of these three studies, the data from Woods et al. [21] were not suitable for meta-analysis because there were no catheter-related adverse events in the MET group. The random effects model revealed a high heterogeneity among the studies (heterogeneity: $\chi^2 = 2.77$, $df = 1$ ($p = 0.10$);

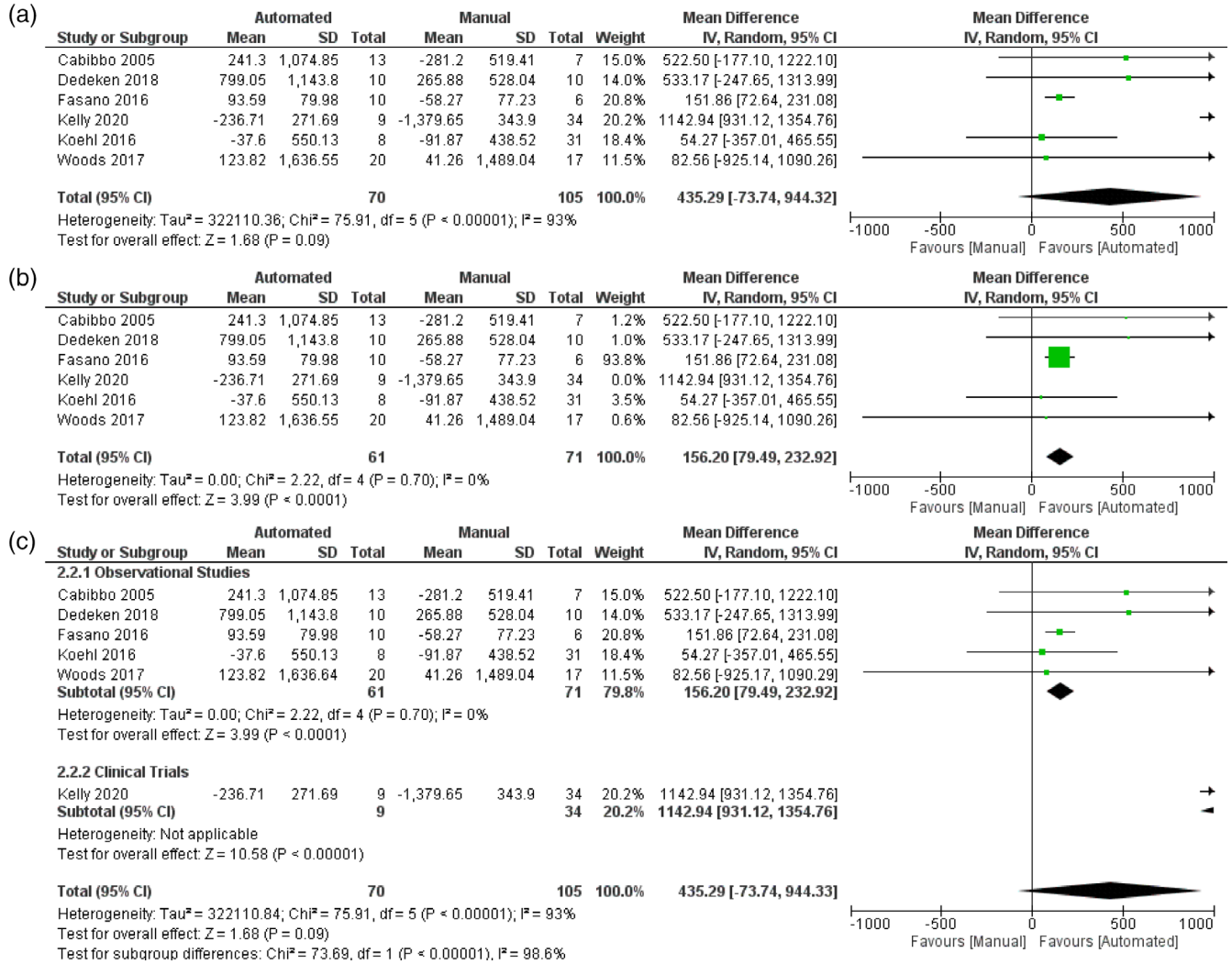

FIGURE 4 Forest plot comparing mean difference in serum ferritin level in automated versus manual red cell exchange procedure (a), after sensitivity analysis excluding Kelly et al. (b), and subgroup analysis for observational studies and clinical trial (c)

$I^2 = 64\%$; $n = 58$) but it was not significant. The pooled risk ratio of these studies was 0.61 (95% CI: 0.18–2.14; $Z = 0.77$; $p = 0.44$), showing no significant increase in the risk of these complications with the erythrocytapheresis procedure (Figure 5d).

Publication bias in included studies

There was no obvious publication bias within the review process as seen from the funnel plot (Figure 6), which was almost symmetrical. The assessment of publication bias using the Begg and Mazumdar rank correlation test showed Kendall's tau value of 0.164 (with continuity correction) with a two-tailed *p*-value of 0.87, which is not significant.

Certainty of evidence

Details of the effect estimates and GRADE ratings are summarized in Table S3. Compared with the control, the certainty of evidence was found to be high for HbS percentage reduction. Therefore, we are very confident that the estimated effect and the true effect lie very close. For serum ferritin level attenuation, the certainty of evidence was found to be low, suggesting that our confidence in the effect estimate was limited and that the true effect might be substantially different from the estimate of the effect.

DISCUSSION

Blood transfusion is the mainstay of therapy in preventing complications, especially primary and secondary strokes, in SCD patients [32]. However, the optimal transfusion remains to be determined. More importantly, the comparison between manual and aRBX and their benefit in SCD in preventing complications have been hardly recognized in the literature. In this meta-analysis, we tried to perform a comparative evaluation of the efficacy of aRBX over MET in attenuating the post-exchange sickled HbS and reducing the iron overload, as well as the safety profile in SCD.

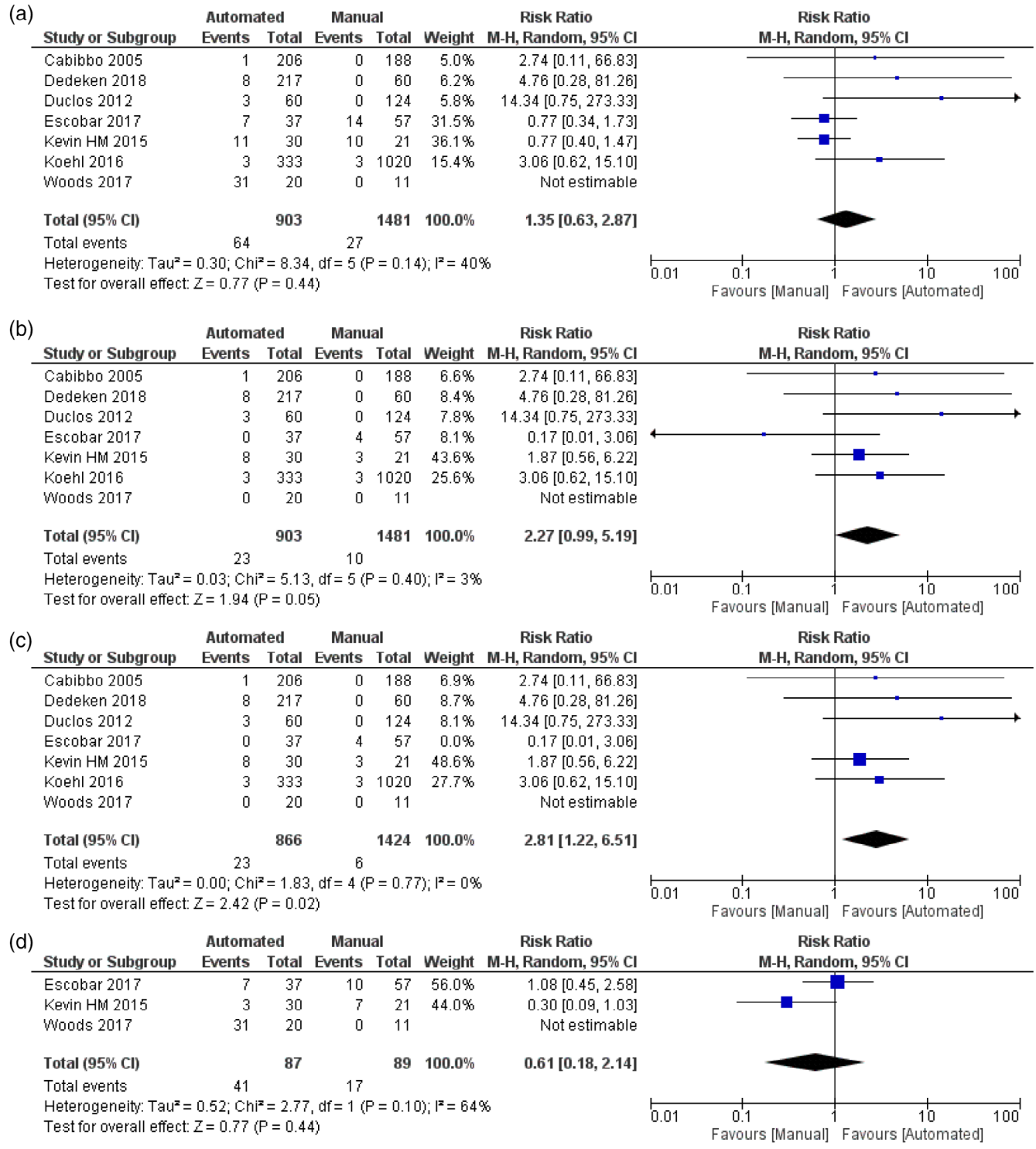

FIGURE 5 Forest plot comparing risk ratio of total adverse events in automated versus manual red cell exchange procedure (a), comparison of the risk ratio of procedure-related adverse events in automated versus manual red cell exchange procedure (b), after sensitivity analysis excluding Escobar et al. (c), and comparison of the risk ratio of catheter-related adverse events in automated versus manual red cell exchange procedure (d)

Percentage HbS level

The result of the present meta-analysis showed no significant reduction in HbS level in the aRBX group [7, 8, 10, 13, 20, 22]. When the result was compared with those of individual studies in the meta-analysis, the trend of the individual study showed HbS reduction towards the aRBX arm, except in the study by Kelly et al. [20], which showed less reduction of HbS in the aRBX arm compared to MET. However,

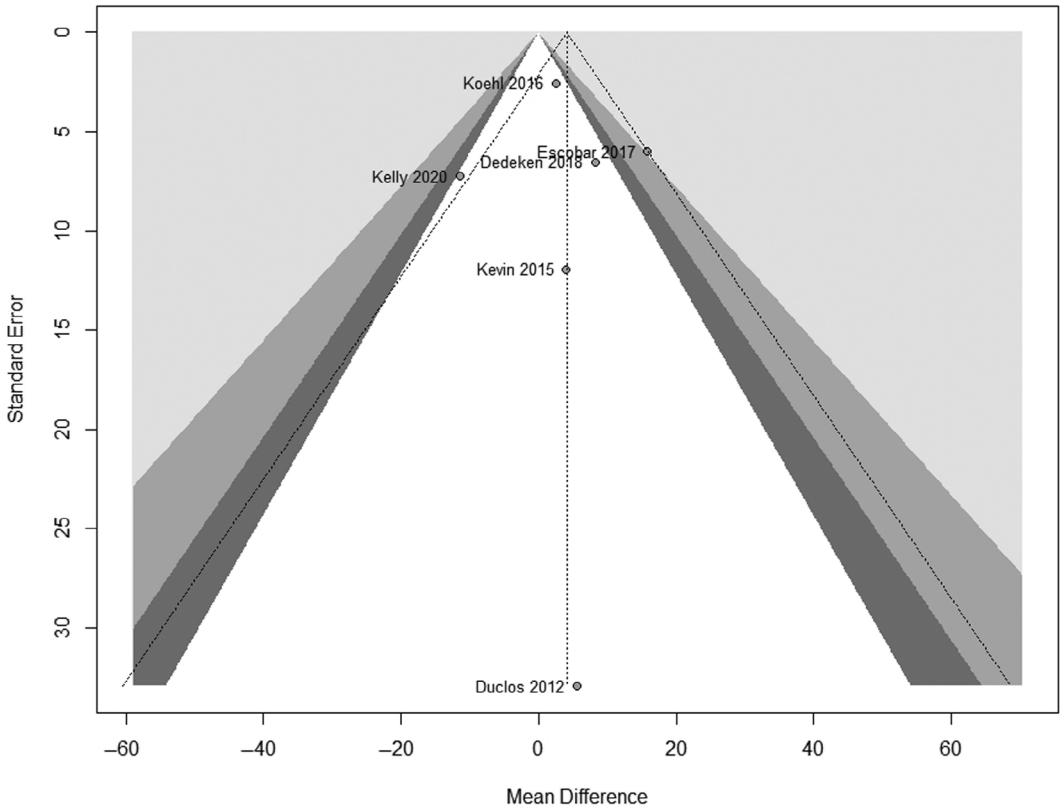

FIGURE 6 Contour-enhanced funnel plot of effect estimate (mean difference of change in HbS level) against standard error

sensitivity analysis by excluding the study of Kelly et al. showed significant reduction of the HbS level in the aRBX group. Subgroup analysis indicated a significant difference between the observational studies and clinical trials. The higher reduction of HbS level in the MET arm observed in the study by Kelly et al. could be due to fewer patients recruited into the aRBX group than the MET group ($n = 9$ in aRBX vs. $n = 34$ in MET). Accordingly, the number of aRBX procedures might be much less than that of MET.

The recommendation to maintain an HbS level below 30% immediately before the next transfusion was largely derived from STOP (Stroke Prevention in Sickle Cell Anaemia) and STOP2 trials and the SWiTCH (Stroke With Transfusions Changing to Hydroxyurea) trial [33–35]. But, it is difficult to comply with the recommendations because the literature frequently reported higher pre-exchange HbS levels [13, 22]. Improving the pre-exchange HbS level by MET may be a formidable task, as the duration of the manual exchange session would be very long, which might increase the risk of hypotension and syncope [22]. aRBX has the advantage to circumvent all these issues, as it could achieve the target pre-exchange HbS level in cases with low baseline haematocrit or in those who were not able to achieve the target HbS consistently by MET [22]. However, Dedeken et al. experienced a significant increase of median HbS (33.5% on MET compared to 45% on aRBX; $p < 0.001$) in 10 patients who were switched from MET to aRBX and had shorter intervals between the procedures while on MET [10]. Woods et al. found that the achievement of HbS goal was not significantly associated with the transfusion mode. Although their study showed a trend towards meeting more frequently the pre-transfusion HBS target with aRBX, the adherence to scheduled transfusion appointments was an important factor contributing to achieving the pre-transfusion HbS goal [21].

Serum ferritin level

In terms of attenuating the serum ferritin level following the intervention of exchange transfusion, we observed that patients who had undergone aRBX had a higher level of serum ferritin reduction compared to those treated with MET. However, there was significant heterogeneity among the studies as revealed in the meta-analysis. The study by Kelly et al. contributed maximum heterogeneity as observed from the sensitivity analysis. Even subgroup analysis showed a significant difference between observational studies and the study by Kelly et al. [20]. Fasano et al. and Kelly et al. reported a significant decline in serum ferritin in patients who underwent aRBX, which was also obvious in our meta-analysis [9, 20]. The possible explanation may be related to chelation adherence: it was observed that patients on MET had been on chelation for a longer duration, and hence had a greater likelihood of chelation mis-adherence [9]. Woods et al. observed that children who received transfusion therapy by aRBX were more adherent to appointments of chelation therapy as well [21]. Therefore, chelation therapy could be a potential confounder, which deserves consideration while analysing the benefit of exchange transfusion [9].

Interestingly, the studies of Woods et al. and Koehl et al. did not find any significant difference in the decline of serum ferritin [7, 21]. Savage et al. and Aloni et al. reported relatively stable serum ferritin levels in children receiving MET [12, 36]. The result of Kelly et al. was distinctly different from those of other studies [20]. Although this study indicated a significant decrease in the risk of excess iron store using aRBX, it did not require adjustment for treatment with or adherence to chelation therapy and any differences in absorption of chelation within the individual. Another strength of this study was that none of the participants was heavily transfused before participating in the study. None of them had a history of regular blood transfusions and had high initial serum ferritin levels. The authors described that the difference between the pre-automatic exchange transfusion and post-automatic exchange transfusion haematocrit is an essential parameter in assessing the benefit of aRBX for lowering the rate of rising serum ferritin. Patients with increased post-transfusion haematocrit will have a positive iron balance. However, there is a lack of guidelines or standards on the post-automatic exchange transfusion haematocrit target value. Hence, patients with low baseline haematocrit are likely to have a positive iron balance following each procedure irrespective of MET or aRBX. The authors observed an increase in ferritin level in children who had lower baseline haemoglobin compared to those who had higher baseline haemoglobin. However, the result was not significant. The comparison of cost effectiveness and duration between red cell exchange by manual and automated methods is shown in Table S1. A meta-analysis of cost effectiveness could not be performed because of inadequate data. Only two studies assessed the cost effectiveness [8, 10] and four studies assessed the duration [8–10, 22], and the results of these studies are contradictory. We searched the literature related to cost effectiveness from SCD-prevalent developing countries as well, but there were no articles comparing the cost effectiveness of manual and automated exchange procedures. The cost effectiveness varies depending on the region and structure of the healthcare system.

Adverse events

Regarding the adverse outcome events due to either red cell exchange procedures, a random effects model analysis from seven included studies [3, 7, 8, 10, 13, 21, 22] did not reveal any significant increase in the risk; however, there was a trend of increased risk of adverse events in the aRBX group. We segregated these adverse events into procedure-related and catheter-related events and performed a separate meta-analysis.

Procedure-related adverse events

The random effects model analysis of procedure-related adverse events showed a trend of increased risk in the aRBCX group. Sensitivity analysis was performed after removing the study by Escobar et al., as only this study reported four adverse events (three hypotension and one transitory hypothermia) during the manual exchange procedure [8]. We found a significant increase in risk related to the aRBX procedure. Cabibbo et al. reported one episode of haemolytic transfusion reaction following exchange transfusion with compatible unit by automated apheresis procedure, but no clinically significant antibody was found. The authors predicted that it could be HLA-antibody-mediated or due to bystander haemolysis (a mechanism of hyperhaemolysis in SCD patients) [3]. Alloimmunization has been frequently encountered in SCD patients with multiple transfusions [37]. However, recent literature shows that the aRBX procedure does not increase the risk of alloimmunization in SCD patients even when donor exposure and blood requirement are higher [38, 39]. Similarly, none of the included studies, except the one by Koehl et al., in our meta-analysis had reported increased incidence of alloimmunization following erythrocytapheresis [7]. Koehl et al. reported three patients who developed alloantibodies out of 39 patients but with no clinically significant antibodies. Furthermore, it was not clear under which group these patients developed alloantibodies [7].

Catheter-related adverse events

Catheter-related complications are the major deterrents of RBX procedures, especially in children. Woods et al. reported 31 events of catheter-related complications, especially catheter-associated thrombosis, infection and mechanical malfunctions in the recipients of aRBX group but not a single incidence of catheter-related complications in the MET group [21]. Catheter-related complications are not uncommon as the Cooperative Study of Sickle Cell Disease found that, by the age of 40, 11.3% of the participants developed catheter-related venous thromboembolism [40]. Catheter stenosis and thrombosis are directly related to the duration of catheter use and the diameter of the catheter [41]. Woods et al. observed that patients in the aRBX group had the catheters inserted for a longer period than MET [21]. In addition, in the aRBX group, double-lumen infusion ports were used, having a larger catheter diameter than the single-lumen infusion ports used for most MET patients, thus possibly increasing the risk of thrombosis. Furthermore, aRBCX needs larger diameter needles to access the port in aRBX than in MET. This might induce a higher risk of catheter malfunction and greater stress of the port's reservoir [42]. In the meta-analysis, we included only three studies for analysis, as only these studies described catheter-related adverse events [8, 21, 22]. The random-effect model revealed high heterogeneity, but the pooled risk ratio showed no significant increased risk of adverse events in the aRBX group. This is possible because in the meta-analysis, the study of Woods et al. could not be analysed as there were no adverse events reported in the manual exchange group [21]. Therefore, data from more such studies are required to arrive at any conclusion regarding adverse events due to RBX procedures. aRBX is preferred over manual exchange, as the latter is less precise and not standardized. Moreover, the manual procedure is prolonged and labour intensive, causing greater discomfort for the patient and therefore poor patient compliance. The automated procedure is more

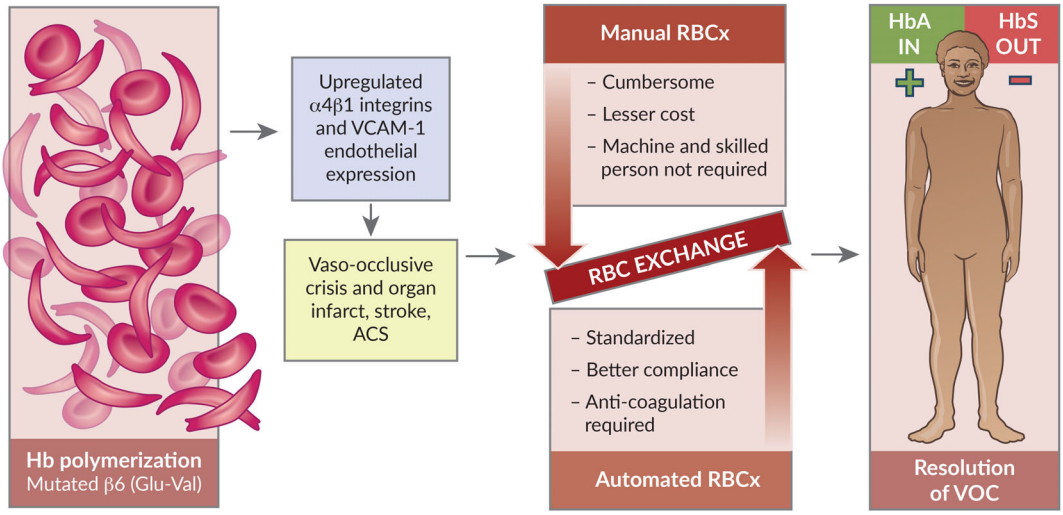

FIGURE 7 Pros and cons of manual versus automated red cell exchange (aRBCx)

efficient in reducing the HbS level (Figure 7). However, it needs an apheresis machine along with costly consumables and skilled personnel [13, 17].

There were a few limitations in our meta-analysis. We could include only nine studies, and most of them were observational and retrospective. Therefore, selection bias and some unclear risk of bias due to improper reporting of the methodology were major drawbacks, resulting in difficulty in suitable comparison between the control and experimental groups. We also could not perform meta-regression analysis from these studies. Also, we recognized that the interval between or frequency of RBX procedures, volume of blood phlebotomized, volume of blood transfused, haematocrit of the transfused unit, pre-exchange and post-exchange haematocrit or haemoglobin of the patient, and pre-transfusion target HbS could potentially impact the outcome of the RBX procedures. However, the data available from the included studies are inconsistent, especially the target HbS values, which vary widely for different clinical conditions in SCD. Nevertheless, to the best of our knowledge, this is the first meta-analysis that compared the efficacy and safety profile of erythrocytapheresis versus manual RBX.

CONCLUSION

In conclusion, this meta-analysis revealed that aRBX did not significantly reduce the HbS and serum ferritin levels when compared with the MET procedure in SCD patients. In terms of adverse events, aRBX also did not show any significant association with the increased risk related to this procedure. Therefore, more high-quality evidence from large randomized controlled trials designed and powered are desirable to reach any conclusion on the efficacy of aRBX over MET as well as on the safety profile of aRBX in both children and adult patients with SCD.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

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SUPPORTING INFORMATION

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