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Interventions for prophylaxis of hepatic veno-occlusive disease in people undergoing haematopoietic stem cell transplantation (Review)

Cheuk DKL, Chiang AKS, Ha SY, Chan GCF

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TABLE OF CONTENTS

[Intervention Review]

Interventions for prophylaxis of hepatic veno-occlusive disease in people undergoing haematopoietic stem cell transplantation

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ABSTRACT

Background

Hepatic veno-occlusive disease (VOD) is a severe complication after haematopoietic stem cell transplantation (HSCT). Different drugs with different mechanisms of action have been tried in HSCT recipients to prevent hepatic VOD. However, it is uncertain whether high-quality evidence exists to support any prophylactic therapy.

Objectives

We aimed to determine the effects of various prophylactic therapies on the incidence of hepatic VOD, overall survival, mortality, quality of life (QOL), and the safety of these therapies in people undergoing HSCT.

Search methods

We searched the Cochrane Central Registe of Controlled Trials (CENTRAL), MEDLINE, EMBASE, conference proceedings of three international haematology-oncology societies and two trial registries in January 2015, together with reference checking, citation searching and contact with study authors to identify additional studies.

Selection criteria

We included randomised controlled trials (RCTs) comparing prophylactic therapies with placebo or no treatment, or comparing different therapies for hepatic VOD in people undergoing HSCT.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included 14 RCTs. Four trials (612 participants) compared ursodeoxycholic acid with or without additional treatment versus placebo or no treatment or same additional treatment. Two trials (259 participants) compared heparin with no treatment. Two trials (106 participants) compared low molecular weight heparin (LMWH) with placebo or no treatment. One trial (360 participants) compared defibrotide with no treatment. One trial (34 participants) compared glutamine with placebo. Two trials (383 participants) compared fresh frozen plasma (FFP) with or without additional treatment versus no treatment or same additional treatment. One trial (30 participants) compared antithrombin III with heparin versus heparin. One trial compared heparin (47 participants) with LMWH (46 participants) and prostaglandin E1 (PGE1) (47 participants). No trial investigated the effects of danaparoid. The RCTs included participants of both genders with wide age range and disease spectrum undergoing autologous or allogeneic HSCT. Funding was provided by government sources (two studies), research

fund (one study), pharmaceutical companies that manufactured defibrotide and ursodeoxycholic acid (two studies), or unclear source (nine studies). All RCTs had high risk of bias because of lack of blinding of participants and study personnel, or other risks of bias (mainly differences in baseline characteristics of comparison groups).

Results showed that ursodeoxycholic acid may reduce the incidence of hepatic VOD (risk ratio (RR) 0.60, 95% confidence interval (CI) 0.40 to 0.88; number needed to treat for an additional beneficial outcome (NNTB) 15, 95% CI 7 to 50, low quality of evidence), but there was no evidence of difference in overall survival (hazard ratio (HR) 0.83, 95% CI 0.59 to 1.18, low quality of evidence). It may reduce all-cause mortality (RR 0.70, 95% CI 0.50 to 0.99; NNTB 17, 95% CI 8 to 431, low quality of evidence) and mortality due to hepatic VOD (RR 0.27, 95% CI 0.09 to 0.87; NNTB 34, 95% CI 16 to 220, very low quality of evidence). There was no evidence of difference in the incidence of hepatic VOD between treatment and control groups for heparin (RR 0.47, 95% CI 0.18 to 1.26, very low quality of evidence), LMWH (RR 0.27, 95% CI 0.06 to 1.18, very low quality of evidence), defibrotide (RR 0.62, 95% CI 0.38 to 1.02, low quality of evidence), glutamine (no hepatic VOD in either group, very low quality of evidence), FFP (RR 0.66, 95% CI 0.20 to 2.17, very low quality of evidence), antithrombin III (RR 0.13, 95% CI 0.01 to 2.15, very low quality of evidence), between heparin and LMWH (RR 1.96, 95% CI 0.80 to 4.77, very low quality of evidence), between heparin and PGE1 (RR 1.20, 95% CI 0.58 to 2.50, very low quality of evidence), and between LMWH and PGE1 (RR 0.61, 95% CI 0.24 to 1.55, very low quality of evidence). There was no evidence of difference in survival between treatment and control groups for heparin (92.6% vs. 88.7%) and defibrotide (HR 1.04, 95% CI 0.54 to 2.02, low quality of evidence). There were no data on survival for trials of LMWH, glutamine, FFP, antithrombin III, between heparin and LMWH, between heparin and PGE1, and between LMWH and PGE1. There were no data on quality of life (QoL) for any trials. Eleven trials reported adverse events. There was no evidence of difference in the frequency of adverse events between treatment and control groups except for one trial showing that defibrotide resulted in more adverse events compared with no treatment (RR 18.79, 95% CI 1.10 to 320.45). These adverse events included coagulopathy, gastrointestinal disorders, haemorrhage and microangiopathy. The quality of evidence was low or very low due to bias of study design, and inconsistent and imprecise results.

Authors' conclusions

There is low or very low quality evidence that ursodeoxycholic acid may reduce the incidence of hepatic VOD, all-cause mortality and mortality due to VOD in HSCT recipients. However, the optimal regimen is not well-defined. There is insufficient evidence to support the use of heparin, LMWH, defibrotide, glutamine, FFP, antithrombin III, and PGE1. Further high-quality RCTs are needed.

PLAIN LANGUAGE SUMMARY

Prevention of occlusion of small veins in the liver after blood-forming stem cell transplantation

Review Question

We reviewed evidence about the effects of medications to prevent blockage of small veins in the liver (veno-occlusive disease or VOD) in people who undergo blood-forming stem cell transplantation (HSCT).

Background

People undergoing HSCT can develop VOD, a severe complication which may lead to their death. Various medications with different mechanisms of action have been tried to prevent VOD. These prophylactic measures include heparin, low molecular weight heparin (LMWH), danaparoid, ursodeoxycholic acid, prostaglandin E1 (PGE1), glutamine, antithrombin III, defibrotide and fresh frozen plasma (FFP). Many transplant centres routinely administer these preventive measures, especially for people at high risk.

Study Characteristics

We included 14 randomised controlled trials (RCTs). Four trials (612 participants) compared ursodeoxycholic acid with or without additional treatment versus placebo or no treatment or the same additional treatment. Two trials (259 participants) compared heparin with no treatment. Two trials (106 participants) compared low molecular weight heparin with placebo or no treatment. One trial (360 participants) compared defibrotide with no treatment. One trial (34 participants) compared glutamine with placebo. Two trials (383 participants) compared fresh frozen plasma with or without additional treatment versus no treatment or the same additional treatment. One trial (30 participants) compared antithrombin III with heparin versus heparin alone. One trial compared heparin (47 participants) with LMWH (46 participants) and prostaglandin E1 (47 participants). No trial investigated the effects of danaparoid. The RCTs included participants of both genders with a wide age range and disease spectrum undergoing HSCT. The evidence is current as of January 2015.

Key Results

Ursodeoxycholic acid may reduce the occurrence of VOD, deaths from all causes and deaths due to VOD, but there was no evidence of a difference in overall survival. There was no evidence of difference in occurrence of VOD between treatment and control groups for heparin, LMWH, defibrotide, glutamine, FFP, antithrombin III, between heparin and LMWH, between heparin and PGE1, and between LMWH and PGE1. There was no evidence of difference in survival between treatment and control groups for heparin and defibrotide. There were no data on survival for trials of LMWH, glutamine, FFP, antithrombin III, between heparin and LMWH, between heparin and PGE1, and between LMWH and PGE1. There were no data on quality of life for any trials. Eleven trials reported adverse effects. There was no evidence

of a difference in adverse events among treatment groups, except for one trial showing that defibrotide resulted in more adverse events compared with no treatment.

Quality of the Evidence

The quality of evidence for all outcomes was low to very low, because of high risk of bias in study design, results inconsistent across studies and imprecision of results.

Conclusion

There is low or very low quality evidence that ursodeoxycholic acid may reduce the incidence of hepatic VOD, overall mortality and mortality due to VOD in people undergoing HSCT. However, the most effective treatment is not well-defined. There is insufficient evidence to support the use of heparin, low molecular weight heparin, defibrotide, glutamine, FFP, antithrombin III, and prostaglandin E1. Further high-quality research is needed.

Summary of findings for the main comparison. Summary of findings: Ursodeoxycholic acid versus placebo or no treatment

Ursodeoxycholic acid compared with placebo or no treatment for prophylaxis of hepatic veno-occlusive disease

Patient or population: People undergoing stem cell transplant with a variety of malignant and non-malignant diseases

Settings: Inpatients

Intervention: Ursodeoxycholic acid

Comparison: Placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no treatment	Ursodeoxycholic acid				
Incidence of hepatic veno-occlusive disease (follow-up: 24 weeks to 1 year)	**189 per 1000[3]**	**113 per 1000** (75 to 167)	**RR 0.60** (0.40 to 0.88)	612 (4)	⊕⊕⊖⊖ **low[1]**	
Overall survival (follow-up: 1 year)	**594 per 1000[3]**	**663 per 1000** (520 to 760)	**HR 0.83** (0.59 to 1.18)	474 (3)	⊕⊕⊖⊖ **low[1]**	
All-cause mortality at 100 days post-transplant (follow-up: 100 days)	**223 per 1000[3]**	**156 per 1000** (111 to 221)	**RR 0.70** (0.50 to 0.99)	612 (4)	⊕⊕⊖⊖ **low[1]**	
Mortality attributable to hepatic veno-occlusive disease (follow-up: 24 weeks to 1 year)	**38 per 1000[3]**	**10 per 1000** (3 to 33)	**RR 0.27** (0.09 to 0.87)	612 (4)	⊕⊖⊖⊖ **very low[2]**	
Quality of life	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Frequency of adverse events	**27 per 1000[4]**	**24 per 1000** (9 to 60)	**RR 0.90** (0.37 to 2.22)	612 (4)	⊕⊖⊖⊖ **very low[2]**	

(follow-up: 24 weeks to 1 year)

*The **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Evidence from RCT downgraded by 2 levels because of high risk of bias in study design (serious) and heterogeneity among the studies (serious)
2. Evidence from RCT downgraded by 3 levels because of high risk of bias in study design (serious), heterogeneity among the studies (serious) and imprecision of results (serious)
3. The assumed risk is the median control group risk across studies
4. The assumed risk is the average of control group risk across studies as three out of four control group risks are zero

Summary of findings 2. Summary of findings: Heparin versus no treatment

Heparin compared with no treatment for prophylaxis of hepatic veno-occlusive disease

Patient or population: People undergoing autologous or HLA identical allogeneic bone marrow transplant with a variety of malignant diseases or aplastic anaemia

Settings: Inpatients

Intervention: Heparin

Comparison: No treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Heparin				
Incidence of hepatic veno-occlusive disease (follow-up: 100 days)	**80 per 1000[4]**	**38 per 1000** (14 to 101)	**RR 0.47** (0.18 to 1.26)	259 (2)	⊕⊖⊖⊖ **very low[1]**	
Overall survival (follow-up: 100 days)	**887 per 1000[4]**	**926 per 1000**	**HR 0.65**	161 (1)	⊕⊖⊖⊖ **very low[2]**	Data were not available for calculation of confidence intervals

All-cause mortality at 100 days post-transplant (follow-up: 100 days)	**113 per 1000**[4]	**75 per 1000** (28 to 199)	**RR 0.66** (0.25 to 1.76)	161 (1)	⊕⊕⊖⊖ **low**[3]	
Mortality attributable to hepatic veno-occlusive disease (follow-up: 100 days)	**88 per 1000**[4]	**25 per 1000** (5 to 199)	**RR 0.28** (0.06 to 1.32)	161 (1)	⊕⊕⊖⊖ **low**[3]	
Quality of life	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Frequency of adverse events (follow-up: 100 days)	**0 per 1000**[4]	**37 per 1000**	**RR 6.91** (0.36 to 131.75)	161 (1)	⊕⊖⊖⊖ **very low**[2]	Control group risk (and assumed risk) is zero. Corresponding risk is based on treatment group risk.

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Evidence from RCT downgraded by 3 levels because of high risk of bias in study design (serious), heterogeneity among the studies (serious) and imprecision of results (serious)
2. Evidence from RCT downgraded by 3 levels because of high risk of bias in study design (serious) and gross imprecision of results (very serious)
3. Evidence from RCT downgraded by 2 levels because of high risk of bias in study design (serious) and imprecision of results (serious)
4. The assumed risk is the median control group risk across studies

Summary of findings 3. Summary of findings: Low molecular weight heparin versus placebo or no treatment

Low molecular weight heparin compared with placebo or no treatment for prophylaxis of hepatic veno-occlusive disease

Patient or population: People undergoing stem cell transplant with malignant diseases

Settings: Inpatients

Intervention: Low molecular weight heparin

Comparison: Placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no treatment	Low molecular weight heparin				
Incidence of hepatic veno-occlusive disease (follow-up: unclear)	**318 per 1000**[2]	**86 per 1000** (19 to 376)	**RR 0.27** (0.06 to 1.18)	45 (1)	⊕⊖⊖⊖ **very low**[1]	
Overall survival	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
All-cause mortality at 100 days post-transplant	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Mortality attributable to hepatic veno-occlusive disease	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Quality of life	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Frequency of adverse events (follow-up: unclear)	**242 per 1000**[2]	**179 per 1000** (65 to 484)	**RR 0.74** (0.27 to 2.00)	61 (1)	⊕⊖⊖⊖ **very low**[1]	

*The basis for the **assumed risk** is the control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Evidence from RCT downgraded by 3 levels because of high risk of bias in study design (serious) and gross imprecision of results (very serious).
2. The assumed risk is the control group risk

Summary of findings 4. Summary of findings: Defibrotide versus no treatment

Defibrotide compared with no treatment for prophylaxis of hepatic veno-occlusive disease

Patient or population: Children undergoing stem cell transplant with malignant and non-malignant diseases and risk factors for hepatic veno-occlusive disease

Settings: Inpatients

Intervention: Defibrotide

Comparison: No treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Defibrotide				
Incidence of hepatic veno-occlusive disease (follow-up: 180 days)	**196 per 1000**[3]	**122 per 1000** (74 to 200)	**RR 0.62** (0.38 to 1.02)	360 (1)	⊕⊕⊖⊖ **low**[1]	
Overall survival (follow-up: 180 days)	**903 per 1000**[3]	**899 per 1000** (804 to 948)	**HR 1.04** (0.54 to 2.02)	356 (1)	⊕⊕⊖⊖ **low**[1]	
All-cause mortality at 100 days post-transplant (follow-up: 100 days)	**95 per 1000**[3]	**100 per 1000** (53 to 188)	**RR 1.05** (0.56 to 1.97)	360 (1)	⊕⊕⊖⊖ **low**[1]	
Mortality attributable to hepatic veno-occlusive disease (follow-up: 180 days)	**56 per 1000**[3]	**22 per 1000** (7 to 70)	**RR 0.40** (0.13 to 1.24)	360 (1)	⊕⊕⊖⊖ **low**[1]	
Quality of life	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Frequency of adverse events (follow-up: 180 days)	**0 per 1000**[3]	**50 per 1000**	**RR 18.79** (1.10 to 320.45)	360 (1)	⊕⊖⊖⊖ **very low**[2]	Control group risk (and assumed risk) is zero. Corresponding risk is based

on treatment group risk.

*The basis for the **assumed risk** is the control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Evidence from RCT downgraded by 2 levels because of high risk of bias in study design (serious) and imprecision of results (serious)
2. Evidence from RCT downgraded by 3 levels because of high risk of bias in study design (serious) and gross imprecision of results (very serious)
3. The assumed risk is the control group risk

Summary of findings 5. Summary of findings: Glutamine versus placebo

Glutamine compared with placebo for prophylaxis of hepatic veno-occlusive disease

Patient or population: People undergoing stem cell transplant with haematological malignancies

Settings: Inpatients

Intervention: Glutamine

Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Glutamine				
Incidence of hepatic veno-occlusive disease (follow-up: till discharge from BMT unit)	**0 per 1000[2]**	**0 per 1000**	**RR not estimable**	34 (1)	⊕⊖⊖⊖ **very low[1]**	No participant developed hepatic veno-occlusive disease in either the treatment or control groups

Overall survival	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
All-cause mortality at 100 days post-transplant (follow-up: 100 days)	**63 per 1000**[2]	**19 per 1000** (0 to 431)	**RR 0.30** (0.01 to 6.84)	34 (1)	⊕⊖⊖⊖ **very low**[1]	
Mortality attributable to hepatic veno-occlusive disease (follow-up: till discharge from BMT unit)	**0 per 1000**[2]	**0 per 1000**	**RR not estimable**	34 (1)	⊕⊖⊖⊖ **very low**[1]	No participant developed hepatic veno-occlusive disease in either the treatment or control groups
Quality of life	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Frequency of adverse events (follow-up: till discharge from BMT unit)	**0 per 1000**[2]	**56 per 1000**	**RR 2.68** (0.12 to 61.58)	34 (1)	⊕⊖⊖⊖ **very low**[1]	Control group risk (and assumed risk) is zero. Corresponding risk is based on treatment group risk.

*The basis for the **assumed risk** is the control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Evidence from RCT downgraded by 3 levels because of high risk of bias in study design (serious) and gross imprecision of results (very serious)
2. The assumed risk is the control group risk

Summary of findings 6. Summary of findings: Fresh frozen plasma versus no treatment

Fresh frozen plasma compared with no treatment for prophylaxis of hepatic veno-occlusive disease

Patient or population: People undergoing stem cell transplants with malignant and non-malignant diseases

Settings: Inpatients

Intervention: Fresh frozen plasma

Comparison: no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Fresh frozen plasma				
Incidence of hepatic veno-occlusive disease (follow-up: 28-100 days)	**78 per 1000**[2]	**51 per 1000** (15 to 170)	**RR 0.66** (0.20 to 2.17)	383 (2)	⊕⊝⊝⊝ **very low**[1]	
Overall survival	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
All-cause mortality at 100 days post-transplant	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Mortality attributable to hepatic veno-occlusive disease	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Quality of life	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Frequency of adverse events	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Evidence from RCT downgraded by 3 levels because of high risk of bias in study design (serious), heterogeneity among the studies (serious) and imprecision of results (serious)
2. The assumed risk is the control group risk

Summary of findings 7. Summary of findings: Antithrombin III plus heparin versus heparin alone

Antithrombin III plus heparin compared with heparin alone for prophylaxis of hepatic veno-occlusive disease

Patient or population: People undergoing stem cell transplant with malignant and non-malignant diseases

Settings: Inpatients

Intervention: Antithrombin III plus heparin

Comparison: Heparin alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Heparin alone	Antithrombin III plus heparin				
Incidence of hepatic veno-occlusive disease (follow-up: unclear)	**250 per 1000[2]**	**33 per 1000** (2 to 538)	**RR 0.13** (0.01 to 2.15)	30 (1)	⊕⊖⊖⊖ **very low[1]**	
Overall survival	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
All-cause mortality at 100 days post-transplant	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Mortality attributable to hepatic veno-occlusive disease (follow-up: unclear)	**0 per 1000[2]**	**0 per 1000**	**RR not estimable**	30 (1)	⊕⊖⊖⊖ **very low[1]**	No participant died of hepatic veno-occlusive disease in either the treatment or control groups
Quality of life	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Frequency of adverse events (follow-up: unclear)	**250 per 1000[2]**	**73 per 1000** (10 to 568)	**RR 0.29** (0.04 to 2.27)	30 (1)	⊕⊖⊖⊖ **very low[1]**	

*The basis for the **assumed risk** is the control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Evidence from RCT downgraded by 3 levels because of high risk of bias in study design (serious) and gross imprecision of results (very serious)
2. The assumed risk is the control group risk

Summary of findings 8. Summary of findings: Heparin versus low molecular weight heparin

Heparin compared with low molecular weight heparin for prophylaxis of hepatic veno-occlusive disease

Patient or population: Patients undergoing stem cell transplant with malignant and non-malignant diseases

Settings: Inpatients

Intervention: Heparin

Comparison:Low molecular weight heparin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Low molecular weight heparin	Heparin				
Incidence of hepatic veno-occlusive disease (follow-up: unclear)	**130 per 1000[2]**	**255 per 1000** (104 to 621)	**RR 1.96** (0.80 to 4.77)	93 (1)	⊕⊖⊖⊖ **very low[1]**	
Overall survival	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
All-cause mortality at 100 days post-transplant	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	
Mortality attributable to hepatic veno-occlusive disease (follow-up: unclear)	**0 per 1000[2]**	**21 per 1000**	**RR 2.94** (0.12 to 70.30)	93 (1)	⊕⊖⊖⊖ **very low[1]**	Control group risk (and assumed risk) is zero. Corresponding risk is based on treatment group risk.

Quality of life	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**
Frequency of adverse events (follow-up: unclear)	**152 per 1000**[2]	**128 per 1000** (45 to 352)	**RR 0.84** (0.30 to 2.31)	93 (1)	⊕⊝⊝⊝ **very low**[1]

*The basis for the **assumed risk** is the control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Evidence from RCT downgraded by 3 levels because of high risk of bias in study design (serious) and gross imprecision of results (very serious)
2. The assumed risk is the control group risk

Summary of findings 9. Summary of findings: Heparin versus prostaglandin E1

Heparin compared with prostaglandin E1 for prophylaxis of hepatic veno-occlusive disease

Patient or population: Patients undergoing stem cell transplant with malignant and non-malignant diseases

Settings: Inpatients

Intervention: Heparin

Comparison: Prostaglandin E1

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Prostaglandin E1	**Heparin**				
Incidence of hepatic veno-occlusive disease (follow-up: unclear)	**213 per 1000**[2]	**255 per 1000** (123 to 533)	**RR 1.20** (0.58 to 2.50)	94 (1)	⊕⊝⊝⊝ **very low**[1]	
Overall survival	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**	

All-cause mortality at 100 days post-transplant	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**
Mortality attributable to hepatic veno-occlusive disease (follow-up: unclear)	**43 per 1000**[2]	**22 per 1000** (2 to 230)	**RR 0.50** (0.05 to 5.33)	94 (1)	⊕⊝⊝⊝ **very low**[1]
Quality of life	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**
Frequency of adverse events (follow-up: unclear)	**298 per 1000**[2]	**128 per 1000** (53 to 304)	**RR 0.43** (0.18 to 1.02)	94 (1)	⊕⊝⊝⊝ **very low**[1]

*The basis for the **assumed risk** is the control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Evidence from RCT downgraded by 3 levels because of high risk of bias in study design (serious) and gross imprecision of results (very serious)
2. The assumed risk is the control group risk

Summary of findings 10. Summary of findings: Low molecular weight heparin versus prostaglandin E1

Low molecular weight heparin compared with prostaglandin E1 for prophylaxis of hepatic veno-occlusive disease

Patient or population: People undergoing stem cell transplant with malignant and non-malignant diseases

Settings: Inpatients

Intervention: Low molecular weight heparin

Comparison: Prostaglandin E1

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				

	Prostaglandin E1	Low molecular weight heparin			
Incidence of hepatic veno-occlusive disease (follow-up: unclear)	**213 per 1000**[2]	**130 per 1000** (51 to 331)	**RR 0.61** (0.24 to 1.55)	93 (1)	⊕⊝⊝⊝ **very low**[1]
Overall survival	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**
All-cause mortality at 100 days post-transplant	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**
Mortality attributable to hepatic veno-occlusive disease (follow-up: unclear)	**43 per 1000**[2]	**9 per 1000** (0 to 179)	**RR 0.20** (0.01 to 4.14)	93 (1)	⊕⊝⊝⊝ **very low**[1]
Quality of life	**Not reported**	**Not applicable**	**Not applicable**	**Not reported**	**Not applicable**
Frequency of adverse events (follow-up: unclear)	**298 per 1000**[2]	**152 per 1000** (68 to 343)	**RR 0.51** (0.23 to 1.15)	93 (1)	⊕⊝⊝⊝ **very low**[1]

*The basis for the **assumed risk** is the control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Evidence from RCT downgraded by 3 levels because of high risk of bias in study design (serious) and gross imprecision of results (very serious)
2. The assumed risk is the control group risk

BACKGROUND

Description of the condition

Haematopoietic stem cell transplantation (HSCT) is an important treatment for many different malignant and non-malignant diseases. However, it is associated with various complications which may result in death. Hepatic veno-occlusive disease (VOD), also known as hepatic sinusoidal obstruction syndrome, is one of the major complications of HSCT and is the leading cause of transplant-related mortality. Up to 77% of transplant recipients develop VOD after HSCT when prophylaxis is not given (Coppell 2010), with mortality of around 84% in severe cases despite treatment (Coppell 2010). It can occur following both autologous and allogeneic HSCT, regardless of the stem cell source, type of conditioning, or underlying disease.

Diagnosis of hepatic VOD is based on a constellation of symptoms and signs and serum bilirubin level. The most commonly used diagnostic criteria for hepatic VOD include the Seattle criteria (McDonald 1984), the modified Seattle criteria (McDonald 1993), and the Baltimore criteria (Jones 1987). By the Seattle criteria, hepatic VOD is diagnosed when two or more of the three criteria (jaundice, hepatomegaly with right upper quadrant abdominal pain, ascites or unexplained weight gain or both) are fulfilled. The modified Seattle criteria require occurrence of at least two of the following three events within 20 days post-HSCT: total bilirubin ≥ 2 mg/dL, hepatomegaly or right upper quadrant abdominal pain of hepatic origin, or unexplained weight gain > 2% of baseline because of fluid accumulation. The Baltimore criteria require an elevated total bilirubin level (≥ 2 mg/dL) before day 21 post-HSCT and two of the following three criteria: tender hepatomegaly, weight gain > 5% from baseline, or ascites. The severity of hepatic VOD is usually categorised into three stages: mild, moderate, or severe, depending on adverse effects from hepatic VOD, treatment required, duration of disease, and mortality (McDonald 1993).

The pathogenesis of hepatic VOD is incompletely understood. The clinical manifestations of hepatic VOD are thought to be caused by sinusoidal obstruction with or without occlusion of intrahepatic central venules, resulting from dysfunction of hepatic sinusoidal endothelial cells (SEC) (DeLeve 2002; Helmy 2006). The cause of SEC dysfunction is multifactorial. Many different risk factors for hepatic VOD have been described. Conditioning with busulfan with or without cyclophosphamide (Barker 2003; Cesaro 2005; Cheuk 2007; Lee 2010; McDonald 1993; Song 2006) or conditioning with total body irradiation (Hasegawa 1998; Lee 2010) are reported to be significant risk factors for hepatic VOD. Busulfan has high inter-patient variability in pharmacokinetics and increased exposure correlates with increased risk of hepatic VOD (Krivoy 2008). Metabolites of busulfan or irradiation may deplete the cellular pool of glutathione, which is an essential antioxidant that protects hepatocytes and SEC from free radical damage (Helmy 2006; McDonald 1993). Irradiation also increases tumour necrosis factor alpha, which causes increased capillary permeability and contributes to SEC and hepatocyte dysfunction (Bearman 1995; Hallahan 1989). People of extreme age may have a higher risk of developing hepatic VOD. The reasons are uncertain. In children, the smaller calibre of hepatic venules and relatively high busulfan concentration may predispose them to develop hepatic VOD (Cesaro 2005; Cheuk 2007; Horn 2002). In the elderly, pre-existing hepatic dysfunction and poorer tolerance to hepatotoxic medications may increase their risk of developing hepatic VOD (McDonald 1984; Toh 1999). Transplant for thalassaemia major (Cheuk 2007) may also carry a higher risk for hepatic VOD development. In people with thalassaemia, the pre-existing iron overload and liver dysfunction may predispose them to develop hepatic VOD when additional insults occur, such as a busulfan-containing conditioning regimen (Cheuk 2007). Various malignancies, such as acute leukaemia (Ozkaynak 1991), neuroblastoma (Cesaro 2005; Horn 2002), or advanced malignancies (Hasegawa 1998; Reiss 2002) may also carry a higher risk of hepatic VOD compared with most non-malignant conditions (Song 2006), as the cytotoxic chemotherapy may have caused hepatocyte injury directly or indirectly through release of various cytokines (Bearman 1995; Helmy 2006). Allogeneic HSCT using an unrelated donor (Barker 2003; McDonald 1993; Reiss 2002; Simon 2001) or human leukocyte antigen (HLA)-mismatched donor (Hasegawa 1998; McDonald 1993) also increases the risk of hepatic VOD, because the alloimmune T cells may release cytokines that contribute to liver toxicity, particularly when acute graft-versus-host disease (GVHD) occurs (Antin 1992; Hasegawa 1998).

Since hepatic VOD can cause significant morbidity and mortality, with some risk factors not modifiable and treatment of established or severe hepatic VOD largely unsuccessful, many transplant centres now administer routine prophylactic therapy to prevent the occurrence of hepatic VOD in transplant recipients, especially in high-risk patients. However, the medications and regimens used are highly variable and no widely accepted recommendation or guideline exists.

Description of the intervention

Prophylactic medications that have been used for hepatic VOD in transplant recipients include heparin (Batsis 2006; Feldman 1996; Marsa-Vila 1991; Rosenthal 1996; Song 2006), low molecular weight heparin (Forrest 2003; Or 1996; Styler 1996), danaparoid (Sakaguchi 2010), ursodeoxycholic acid (Essell 1992; Thornley 2004), prostaglandin E1 (Gluckman 1990; Song 2006), glutamine (Brown 1998), and defibrotide (Capelli 2009; Chalandon 2004; Corbacioglu 2006; Dignan 2007; Qureshi 2008; Versluys 2004). Some of these have also been tried in combinations (Simon 2001). Prophylaxis is generally given continuously from the commencement of conditioning or the time of stem cell infusion until neutrophil engraftment, or three to four weeks after HSCT, during which hepatic VOD is most likely to develop. Some centres administer hepatic VOD prophylaxis to all people undergoing HSCT, while others will only give prophylaxis for those at high risk, with variable criteria for 'high risk'.

How the intervention might work

Heparin is an anticoagulant which enhances the action of the natural anticoagulant antithrombin in inhibiting multiple coagulation factors including thrombin, factors VIIa, IXa, Xa, XIa, and XIIa. Prophylactic heparin administration is intended to prevent clot formation in hepatic venules, which is part of the pathological changes in hepatic VOD. Heparin prophylaxis was found to be associated with a low incidence of hepatic VOD in some studies (10% to 20%) (Rosenthal 1996; Song 2006). Survival at 100 days post-transplant was as high as 95% (Song 2006). Mild haemorrhage occurred in 56% of participants in one study (Rosenthal 1996). Combining heparin with fresh frozen plasma might further reduce the incidence of hepatic VOD to 5.9% (Batsis 2006).

Low molecular weight heparin, such as enoxaparin, is a derivative of heparin with a similar mechanism of action. It has the advantage of more predictable and stable anticoagulant effects and thus reduces the need for monitoring. It is injected subcutaneously and does not require continuous intravenous infusion. It is also less likely to cause significant adverse events, such as heparin-induced thrombocytopenia or osteoporosis. Its use was found to be associated with a low incidence of hepatic VOD (4% to 23%) (Forrest 2003; Simon 2001; Styler 1996). Overall survival at 100 days was 85% in one study (Forrest 2003). Minor haemorrhage occurred in 60% of participants and significant haemorrhage occurred in 1% to 8% of participants (Forrest 2003; Simon 2001).

Danaparoid is a mixture of low molecular weight heparin, chondroitin sulfate, and dermatan sulfate present in animal gut mucosa. It renders factor Xa and thrombin inactive without affecting platelet function. It therefore promotes anticoagulation with a lower bleeding tendency than heparin or low molecular weight heparin. It also inhibits inflammatory cytokines (Iba 2008) and may reduce the incidence of hepatic VOD (Sakaguchi 2010). Only 2% of people developed hepatic VOD and 2% had significant haemorrhage (Sakaguchi 2010).

Ursodeoxycholic acid is a hydrophilic bile acid which alters the milieu of bile acids by making them less hydrophobic overall. Since retention of hydrophobic bile acids was thought to contribute to hepatocellular injury in cholestatic liver disease, ursodeoxycholic acid might reduce hepatotoxicity induced by hepatotoxic medications used during HSCT. Moreover, ursodeoxycholic acid may attenuate the pro-inflammatory cytokine environment through decreased expression of tumour necrosis factor alpha, interleukin 1, interleukin 2, and interferon gamma, thereby minimising endothelial injury (Yoshikawa 1992). Ursodeoxycholic acid was found to prevent hepatic VOD in some clinical studies (Essell 1992; Thornley 2004). The incidence of hepatic VOD ranged from 3% to 9% (Essell 1992; Thornley 2004). The overall survival at four years was 70% (Thornley 2004). No adverse event was reported.

Prostaglandin E1 is a vasodilator with inhibitory effects on platelet aggregation, which may therefore prevent clotting of the hepatic venules and prevent hepatic VOD from developing or progressing. Some studies showed that continuous prostaglandin E1 administration was associated with reduced incidence of hepatic VOD (Gluckman 1990; Lee 2010; Song 2006). Hepatic VOD occurred in 12% to 35% of participants (Gluckman 1990; Song 2006) and survival at 100 days post-transplant was 92% to 95% in one study (Song 2006). No adverse effect was reported.

Glutamine is the precursor for production of glutathione, which is an essential antioxidant that protects hepatocytes and endothelial cells from oxidative damage by free radicals and activated chemotherapeutic metabolites (Teicher 1988). Glutamine becomes the rate-limiting factor in the production of glutathione by the liver during periods of catabolic stress. Glutathione depletion is hypothesised to be an essential component in the pathogenesis of hepatic VOD (Helmy 2006). By increasing production of glutathione, glutamine may prevent the development of hepatic VOD. Glutamine supplementation has led to preservation of protein C and albumin levels early in the post-transplant period, which may be associated with a reduced risk of hepatic VOD (Brown 1998). Among 18 participants who received glutamine, none developed hepatic VOD and all survived the initial post-transplant period (Brown 1998). No adverse event was reported.

Defibrotide is a mixture of single-stranded oligonucleotide. It binds to endothelial cells via adenosine receptors A1 and A2 (Bianchi 1993), which may protect endothelial cells in response to injury. It increases endogenous production of prostaglandin I2, prostaglandin E2 (Coccheri 1988), and thrombomodulin (Zhou 1994), which inhibit platelet activities and coagulation. It also decreases thrombin generation and thrombin-induced platelet aggregation (Bracht 1994), and promotes fibrinolysis via upregulation of tissue factor pathway inhibitor (Cella 2001) and tissue plasminogen activator (Falanga 2003; Pasini 1996), reduction of plasminogen activator inhibitor 1 (Falanga 2003; Pasini 1996), and enhancement of plasmin activity (Echart 2009). Some clinical studies found defibrotide to be effective in preventing hepatic VOD, which occurred in 0% to 11% of those given prophylaxis (Capelli 2009; Chalandon 2004; Corbacioglu 2006; Dignan 2007; Qureshi 2008; Versluys 2004). Overall survival at 100 days post-transplant ranged from 89% to 100% (Chalandon 2004; Corbacioglu 2006; Dignan 2007; Versluys 2004). No adverse event was reported.

Why it is important to do this review

Hepatic VOD is a severe complication of haematopoietic stem cell transplantation with high mortality and therefore prevention is an obvious priority. However, it remains uncertain whether the aforementioned preventive medications are based on high-quality evidence. It is therefore important to perform a systematic review to ascertain which medications are effective for prevention of hepatic VOD and to assess the quality of evidence. This is essential for the development of clinical guidelines in the future.

OBJECTIVES

We aimed to determine the effects of various prophylactic therapies on incidence of hepatic VOD, overall survival, mortality, quality of life (QOL), and the safety of these therapies in people undergoing HSCT.

METHODS

Criteria for considering studies for this review

Types of studies

We only include randomised controlled trials (RCTs) in the review.

Types of participants

We include people of all ages who were undergoing haematopoietic stem cell transplantation (HSCT) for any indication.

Types of interventions

We include trials evaluating prophylactic medications for hepatic veno-occlusive disease (VOD) in the review. The interventions might include heparin, low molecular weight heparin, danaparoid, ursodeoxycholic acid, prostaglandin, glutamine, defibrotide, or others. The control interventions could be placebo or no intervention. We also include trials comparing alternative regimens of the same medication or comparing different medications.

Types of outcome measures

We have not used the outcomes listed below as criteria for inclusion of studies.

Primary outcomes

1. Incidence of hepatic VOD (proportion of participants who developed hepatic VOD during the study period)
2. Overall survival (reported as time-to-event data)

Secondary outcomes

- All-cause mortality (proportion of participants who died) (Mortality reported at different time points are analysed separately)
- Mortality attributable to hepatic VOD (proportion of participants who died due to hepatic VOD during the study period)
- Quality of life (measured by any validated scales at any time point after treatment)
- Frequency of adverse events (proportion of participants who experienced adverse effects) (All adverse events, severe adverse events and specific adverse events are analysed separately)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (28 January 2015), MEDLINE (OVID, 1966 to 28 January 2015) and EMBASE (OVID, 1980 to 28 January 2015) (Lefebvre 2011). The search strategies for the different electronic databases (using a combination of controlled vocabulary and text word terms) are shown in the appendices: CENTRAL (Appendix 1), MEDLINE (Appendix 2), and EMBASE (Appendix 3).

Searching other resources

We also searched conference proceedings of the following annual meetings, if not already included in CENTRAL, from 2000 to January 2015:

- American Society of Hematology (ASH);
- American Society for Clinical Oncology (ASCO);
- European Society for Medical Oncology (ESMO).

We also searched:

- the World Health Organization International Clinical Trials Registry Platform (ICTRP) which registers clinical trials from many different countries (apps.who.int/trialsearch) (accessed on 28 January 2015, using search terms 'veno-occlusive disease' or 'sinusoidal obstruction syndrome');
- the meta-register of controlled trials (www.controlled-trials.com/mrct/) (accessed on 28 January 2015, using search terms 'veno-occlusive disease' or 'sinusoidal obstruction syndrome').

We include articles published only in abstract form if the review authors could be contacted to provide essential details for appraisal and analysis. We searched reference lists of relevant articles. Wecontacted authors of included studies to identify possible unpublished studies. There was no language restriction in the search and inclusion of studies. We considered multiple publications reporting the same group of participants or its subsets as a single study.

Data collection and analysis

Selection of studies

Two review authors (DKLC and AKSC) independently reviewed titles and abstracts of references retrieved from the searches and select all potentially relevant studies. The same review authors obtained copies of these articles and reviewed them independently against our pre-defined inclusion criteria (Higgins 2011a). Review authors were not blinded to the names of the trial authors, institutions, or journal of publication. We resolved all disagreements about selection of studies by consensus. We report the flow of studies as per the PRISMA statement in a flow chart, which contains data on the number of records identified through database searching, number of additional records identified through other sources, number of records after duplicates removed, number of records screened, number of records excluded, number of full-text articles examined for eligibility, number of full-text articles excluded with reasons, and numbers of studies included in qualitative and quantitative syntheses.

Data extraction and management

Two review authors (DKLC and AKSC) independently extracted data from included trials and entered them into a data collection form (Higgins 2011a), resolving all disagreements by consensus. We contacted the authors of included studies to provide essential information that was missing from study reports. We extracted the following data when available:

1. Study methods
   a. Randomisation method (including list generation)
   b. Method of allocation concealment
   c. Blinding method
   d. Stratification factor
2. Participants
   a. Inclusion/exclusion criteria
   b. Number (total/per group)
   c. Age and gender distribution
   d. Underlying diseases requiring HSCT
   e. Previous treatments (chemotherapy, radiotherapy, HSCT)
   f. Pre-existing liver dysfunction
   g. Previous history of hepatic VOD
   h. Performance status before transplant
   i. Type of transplant (autologous, allogeneic)
   j. Donor (family donor, unrelated donor)
   k. Human leukocyte antigen (HLA) disparity
   l. Stem cell source (bone marrow, peripheral blood stem cell, cord blood)
   m. Stem cell manipulation (T cell depletion, CD34+ cell selection)
   n. Conditioning regimen
   o. Graft-versus-host disease (GVHD) prophylaxis

3. Intervention and control
   a. Type of prophylactic intervention
   b. Type of control
   c. Details of prophylactic regimen and control
   d. Details of co-interventions
4. Follow-up data
   a. Duration of follow-up
   b. Loss to follow-up with reasons
5. Outcome data as described above
6. Analysis data
   a. Methods of analysis (intention-to-treat or per-protocol analysis)

We entered the data into Review Manager 5 (RevMan) (RevMan 2014).

For overall survival data, we estimated the difference between observed and expected event rate (O-E) and its variance from reported event frequencies, as described by Tierney 2007.

Assessment of risk of bias in included studies

Two review authors (DKLC and AKSC) independently assessed the quality of each eligible trial, resolving all disagreements by consensus.

We included the following items to assess the methodological quality of RCTs in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b):

1. Was the allocation sequence adequately generated?
2. Was allocation adequately concealed?
3. Blinding: was knowledge of the allocated interventions adequately prevented during the study?
4. Were incomplete outcome data adequately addressed?
5. Were reports of the study free of suggestion of selective outcome reporting?
6. Was the study apparently free of other problems that could put it at a high risk of bias?

We planned to conduct sensitivity analyses to assess the impact of risk of bias, by including and excluding studies at high risk of bias.

Measures of treatment effect

We used risk ratio (RR) estimates with 95% confidence intervals (CIs) for binary outcomes. We used hazard ratio (HR) estimates with 95% CI for time-to-event outcomes. We calculated the number needed to treat for an additional beneficial outcome (NNTB) estimates with 95% CI. We used mean difference (MD) estimates with 95% CI for continuous outcome (Deeks 2011). All analyses included all participants in the treatment groups to which they were allocated (intention-to-treat analyses) if data were available.

Dealing with missing data

We contacted the authors of included studies to supply missing data. We assessed missing data and dropouts for each included study and assessed and discussed the extent to which the results or conclusions of the review could be altered by the missing data (Higgins 2011c). If fewer than 70% of participants allocated to the treatments were reported on at the end of the trial for a particular outcome, we considered those data to be prone to bias. We did not impute missing data, except that for mortality and incidence of hepatic VOD data we assumed that participants had not died or developed VOD if their data were missing. Meta-analysis of time-to-event data usually requires availability of individual patient data from the original investigators (Higgins 2011a). Otherwise, we used statistical methods according to Tierney 2007.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of important participant factors between trials (age, underlying diseases, transplant characteristics) and trial factors (randomisation concealment, blinding, losses to follow-up, intervention regimens). We assessed statistical heterogeneity by examining the I^2 statistic (Deeks 2011), a quantity which describes approximately the proportion of variation in point estimates due to heterogeneity rather than to sampling error. We followed the guide on interpretation of the I^2 statistic suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* as follows:

- 0% to 40%: may not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

In addition, we employed a Chi^2 test of homogeneity to determine the strength of evidence that heterogeneity was genuine. If significant heterogeneity ($P < 0.1$) was present, we explored trials to investigate possible explanations.

Assessment of reporting biases

We had planned to draw funnel plots (estimated differences in treatment effects against their standard errors) if we found sufficient studies (at least 10) for a given outcome. Asymmetry could be due to publication bias, but could also be due to a relationship between trial size and effect size. In the event that we found a relationship, we would have examined clinical diversity of the studies (Sterne 2011). However, there were fewer than ten studies reporting the same outcome and we therefore did not draw a funnel plot.

Data synthesis

Where the interventions were the same or similar enough, we synthesised results in a meta-analysis if there was no important clinical heterogeneity. We used the Review Manager 5 software (RevMan 2014) to perform meta-analyses using a fixed-effect model (the generic inverse variance method for continuous data outcomes and the Mantel-Haenszel method for dichotomous data outcomes) (Deeks 2011). For multi-arm studies, we conducted analyses of pair-wise comparisons. For meta-analyses, we did not combine the results from participants of the same study into the same meta-analysis more than once to avoid double counting. There was also no arbitrary omission of relevant groups. We produced 'Summary of findings' tables according to the recommendations in the *Cochrane Handbook* (Deeks 2011). These tables summarise the results for the six pre-defined outcomes (incidence of hepatic VOD, overall survival, all-cause mortality, mortality due to hepatic VOD, quality of life, and frequency of adverse events) and provide grading of the quality of evidence according to the GRADE system (GRADEpro 2008; Schünemann 2011).

Subgroup analysis and investigation of heterogeneity

If data permitted, we conducted subgroup analyses (Deeks 2011) for:

1. Different age groups (younger than 12 years, 12 to 18 years, 18 to 60 years, older than 60 years);
2. Different types of underlying diseases (different disease groups);
3. Different types of transplant (autologous, family donor, unrelated donor);
4. Different HLA parity (HLA-matched, HLA-mismatched);
5. Different transplant conditioning (radiation-based, non-radiation-based, busulfan-containing, non-busulfan-containing).

We defined these subgroups a priori. Participants in these important subgroups might have different susceptibility to hepatic VOD and hence might have different response to prophylactic therapy.

We assessed subgroup differences by examining the I^2 statistic and performing a Chi^2 test for heterogeneity across subgroup results.

Sensitivity analysis

We had planned to conduct sensitivity analyses to assess the impact of study quality (Deeks 2011). These would include:

1. All studies;
2. Only those without high risk of bias in any aspect.

However, since all the included studies had a high risk of bias, we did not perform a sensitivity analysis.

For outcomes with substantial heterogeneity, we would also have performed random-effects meta-analysis as a sensitivity analysis.

RESULTS

Description of studies

Results of the search

The electronic searches retrieved a total of 726 records (89 records from CENTRAL, 500 records from MEDLINE, and 137 records from EMBASE). Searching of Internet sources and conference proceedings retrieved an additional 55 records. After duplicates were removed, 622 records remained and were screened. We obtained 25 full-text records. We excluded one study (Characteristics of excluded studies). Two were ongoing studies (Characteristics of ongoing studies). The remaining 22 records describing 14 studies were included (Characteristics of included studies). The flow of the studies is described in Figure 1.

Figure 1. Study flow diagram.

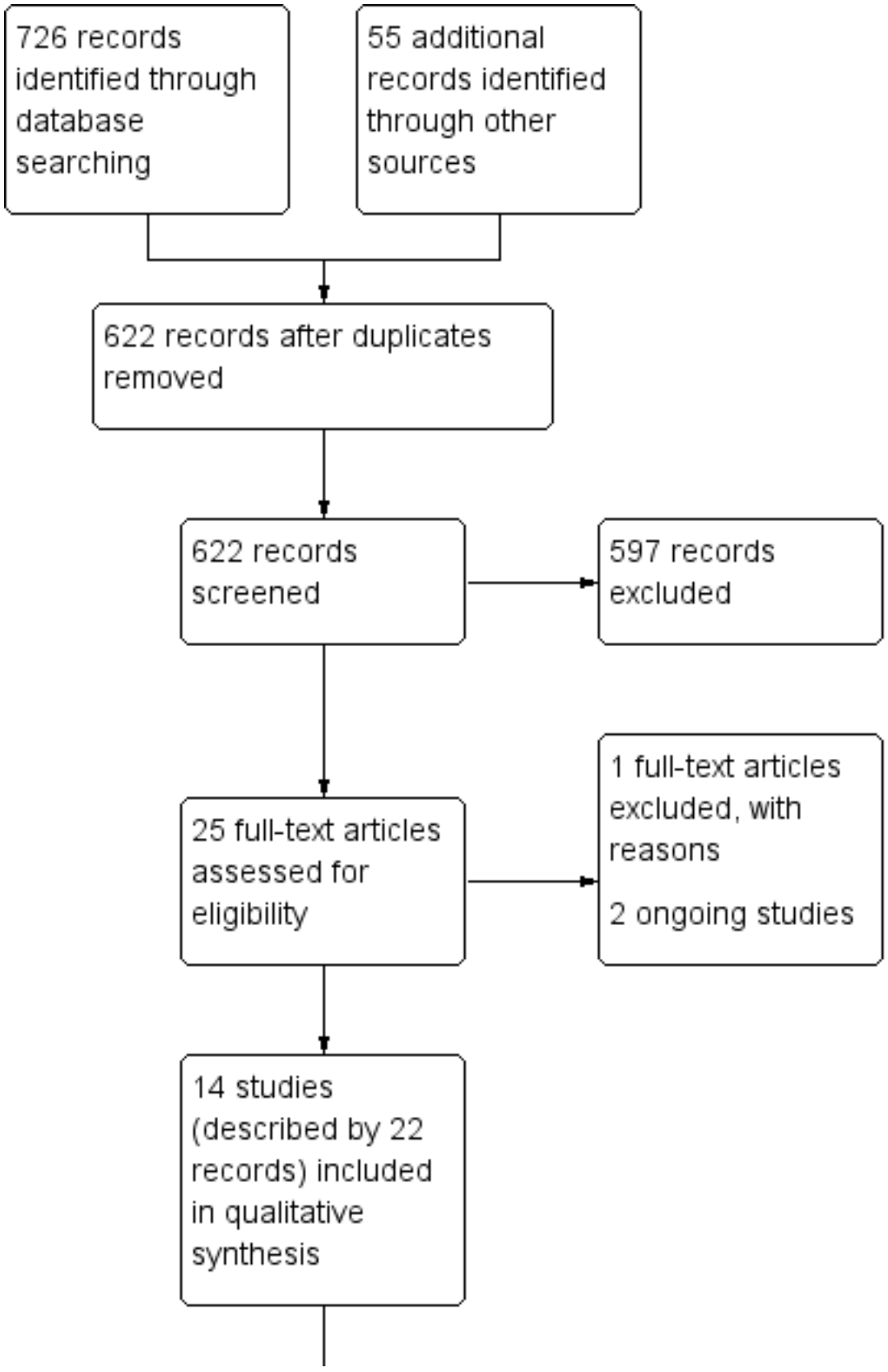
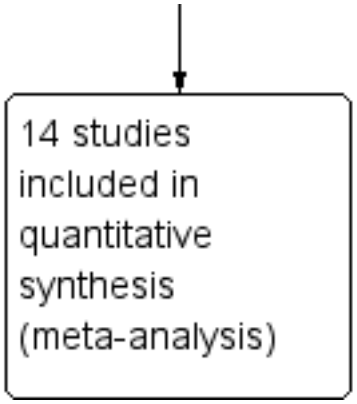


Figure 1. (Continued)



Included studies

Among the 14 included studies, 10 were published as full papers (Attal 1992; Brown 1998; Corbacioglu 2012; Essell 1998; Marsa-Vila 1991; Matsumoto 2007; Ohashi 2000; Or 1996; Park 2002; Ruutu 2002) and four were published as abstracts only (Demuynck 1995; Jung 2005; Lee 1996; Yannaki 2012). We contacted the authors of all studies for missing information but none provided us with useful results. The characteristics are described in the table of Characteristics of included studies and are summarised below. Two studies each were done in France (Attal 1992; Marsa-Vila 1991), Japan (Matsumoto 2007; Ohashi 2000), and Korea (Jung 2005; Park 2002). One study was done in 28 centres in Europe (Corbacioglu 2012). One study was done in Finland and Sweden (Ruutu 2002). One study each was done in USA (Essell 1998), UK (Brown 1998), Belgium (Demuynck 1995), Greece (Yannaki 2012), Israel (Or 1996), and Singapore (Lee 1996). Two studies were funded by government sources (Marsa-Vila 1991; Matsumoto 2007), one study was supported by a research fund (Or 1996), and two studies were funded by pharmaceutical companies which manufactured defibrotide (Corbacioglu 2012) and ursodeoxycholic acid (Essell 1998) respectively. The funding sources of the other studies were unclear.

Design

All included studies were parallel-group randomised controlled trials. Thirteen studies had two comparison groups (Attal 1992; Brown 1998; Corbacioglu 2012; Essell 1998; Jung 2005; Lee 1996; Marsa-Vila 1991; Matsumoto 2007; Ohashi 2000; Or 1996; Park 2002; Ruutu 2002; Yannaki 2012) and one study had three comparison groups (Demuynck 1995).

Sample sizes

The sample size of each included study ranged from 30 to 360 participants. Sample size calculation a priori was performed in six studies (Attal 1992; Corbacioglu 2012; Essell 1998; Ohashi 2000; Park 2002; Ruutu 2002)

Setting

All studies were carried out in the inpatient setting for people undergoing HSCT.

Participants

The 14 included studies recruited a total of 1922 participants. All studies included both men and women in similar proportions. Six studies recruited both adults and children aged from one to 64 years (Attal 1992; Brown 1998; Matsumoto 2007; Or 1996; Ruutu 2002; Yannaki 2012), while four studies recruited adults only (aged 18 to 56 years) (Essell 1998; Ohashi 2000; Marsa-Vila 1991; Park 2002) and one study recruited children only (aged 0 to18 years) (Corbacioglu 2012). In three studies, the age distribution of participants was not clear (Demuynck 1995; Jung 2005; Lee 1996). Nine studies recruited participants with a variety of malignant and non-malignant diseases (Attal 1992; Brown 1998; Corbacioglu 2012; Essell 1998; Jung 2005; Matsumoto 2007; Ohashi 2000; Park 2002; Ruutu 2002), while one study recruited only participants with haematological malignancies (Lee 1996) and two studies recruited only participants with haematological malignancies or solid tumours (Marsa-Vila 1991; Or 1996). The participants' underlying diseases were not described in two studies (Demuynck 1995; Yannaki 2012). Only two studies (Essell 1998; Corbacioglu 2012) described treatments that participants received prior to HSCT. Only one study described the performance status prior to HSCT (Essell 1998). Eleven studies recruited both allogeneic and autologous transplant recipients (Attal 1992; Brown 1998; Corbacioglu 2012; Demuynck 1995; Jung 2005; Lee 1996; Ohashi 2000; Or 1996; Park 2002; Ruutu 2002; Yannaki 2012), while two studies recruited only allogeneic transplant recipients (Essell 1998; Matsumoto 2007) and one study recruited only autologous transplant recipients (Marsa-Vila 1991). Stem cell source was bone marrow exclusively in four studies (Attal 1992; Essell 1998; Lee 1996; Marsa-Vila 1991). Either bone marrow or peripheral blood stem cell was used in two studies (Brown 1998; Ruutu 2002); and cord blood was also used in some participants in three studies (Corbacioglu 2012; Jung 2005; Matsumoto 2007). The stem cell source was not described in five studies (Demuynck 1995; Ohashi 2000; Or 1996; Park 2002; Yannaki 2012). A variety of conditioning regimen was used in nine studies (Attal 1992; Brown 1998; Corbacioglu 2012; Matsumoto 2007; Ohashi 2000; Or 1996; Park 2002; Ruutu 2002; Yannaki 2012). Only busulfan and cyclophosphamide were used in one study (Essell 1998). In four studies (Demuynck 1995; Jung 2005; Lee 1996; Marsa-Vila 1991), authors did not describe the conditioning regimen used. Different GVHD prophylaxis was employed in four studies (Corbacioglu 2012; Matsumoto 2007; Ohashi 2000; Ruutu 2002). In two studies (Attal 1992; Essell 1998), all allogeneic transplant recipients received cyclosporin and methotrexate for

GVHD prophylaxis. In seven studies (Brown 1998; Demuynck 1995; Jung 2005; Lee 1996; Or 1996; Park 2002; Yannaki 2012), GVHD prophylaxis was not described. In one study (Marsa-Vila 1991), only autologous HSCT was performed and GVHD prophylaxis was not applicable. Pre-existing liver dysfunction occurred in some participants in four studies (Attal 1992; Corbacioglu 2012; Essell 1998; Or 1996). This was not described in the remaining ten studies. History of hepatic VOD in participants was described in only one study (Attal 1992).

Interventions

Four studies investigated the efficacy of ursodeoxycholic acid, with two studies comparing ursodeoxycholic acid with placebo (Essell 1998; Ruutu 2002), one study comparing ursodeoxycholic acid with no treatment (Ohashi 2000), and one study comparing ursodeoxycholic acid plus heparin with heparin alone (Park 2002). The dosing regimen of ursodeoxycholic acid was variable among different trials. One included trial used ursodeoxycholic acid at 300 mg twice daily from 12 to 24 hours before conditioning till discharge or day 30 post-transplant (Park 2002). One trial used 600 mg per day from 21 days before stem cell infusion till day 80 post-transplant (Ohashi 2000). One trial used 6 mg/kg twice daily from the day of conditioning till day 90 post-transplant (Ruutu 2002). One trial used different doses depending on body weight categories from before the start of conditioning till day 80 post-transplant (Essell 1998). Two studies compared heparin with no treatment (Attal 1992; Marsa-Vila 1991). The first study (Attal 1992) used heparin at 100 units/kg/day from the start of conditioning till 30 days post-transplant or discharge. The second study (Marsa-Vila 1991) used heparin at 1 mg/kg/day from day 0 to haematological reconstitution and discharge. Two studies investigated the efficacy of low molecular weight heparin, with one study comparing enoxaparin (40 mg daily from one day before stem cell infusion till discharge or day 40 post-transplant) with placebo (Or 1996), and one study comparing nadroparin with no treatment (Lee 1996). One study compared defibrotide (6.25 mg/kg/dose every 6 hours from the day of conditioning till day 30 post-transplant) with no treatment (Corbacioglu 2012). One study compared glutamine (50 g daily from the start of conditioning till discharge from the transplant unit) with placebo (Brown 1998). One study compared fresh frozen plasma (FFP) (dosage according to body weight, twice weekly from conditioning till day 28 post-transplant) with no treatment (Matsumoto 2007), and one study compared FFP plus heparin with heparin alone (Yannaki 2012). One study compared antithrombin III (1000 units twice daily from day one till day 14 post-transplant) plus heparin with heparin alone (Jung 2005). The three-arm study compared heparin (100 units/kg/day) with enoxaparin (20 mg/day) and prostaglandin E1 (PGE1) (500 microgram/kg/day) (Demuynck 1995). No trial investigated the effects of danaparoid.

Outcomes

Thirteen studies reported the incidence of hepatic veno-occlusive disease (VOD) as an outcome measure (Attal 1992; Brown 1998; Corbacioglu 2012; Demuynck 1995; Essell 1998; Jung 2005; Lee 1996; Marsa-Vila 1991; Matsumoto 2007; Ohashi 2000; Park 2002; Ruutu 2002; Yannaki 2012). One study did not report the incidence of hepatic VOD, but frequencies of individual symptom or sign of hepatic VOD in participants, including hyperbilirubinaemia, hepatic enlargement, right upper quadrant abdominal pain, ascites, and weight gain (Or 1996). Five studies reported overall survival (Attal 1992; Corbacioglu 2012; Essell 1998; Park 2002; Ruutu 2002). Six studies reported all-cause mortality (Brown 1998; Corbacioglu 2012; Essell 1998; Ohashi 2000; Park 2002; Ruutu 2002) and nine studies reported mortality attributable to hepatic VOD (Attal 1992; Brown 1998; Corbacioglu 2012; Demuynck 1995; Essell 1998; Jung 2005; Ohashi 2000; Park 2002; Ruutu 2002). None of the 14 included studies reported quality of life of participants. Eleven studies reported adverse events (Attal 1992; Brown 1998; Corbacioglu 2012; Demuynck 1995; Essell 1998; Jung 2005; Lee 1996; Ohashi 2000; Or 1996; Park 2002; Ruutu 2002), which were mainly bleeding complications.

Excluded studies

We excluded one study after examining the full text of the published reports (Characteristics of excluded studies). This study was evaluating treatment of hepatic VOD instead of prophylaxis (Carbacioglu 2004).

Risk of bias in included studies

The distribution of risk of bias in different aspects of the included studies is shown in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

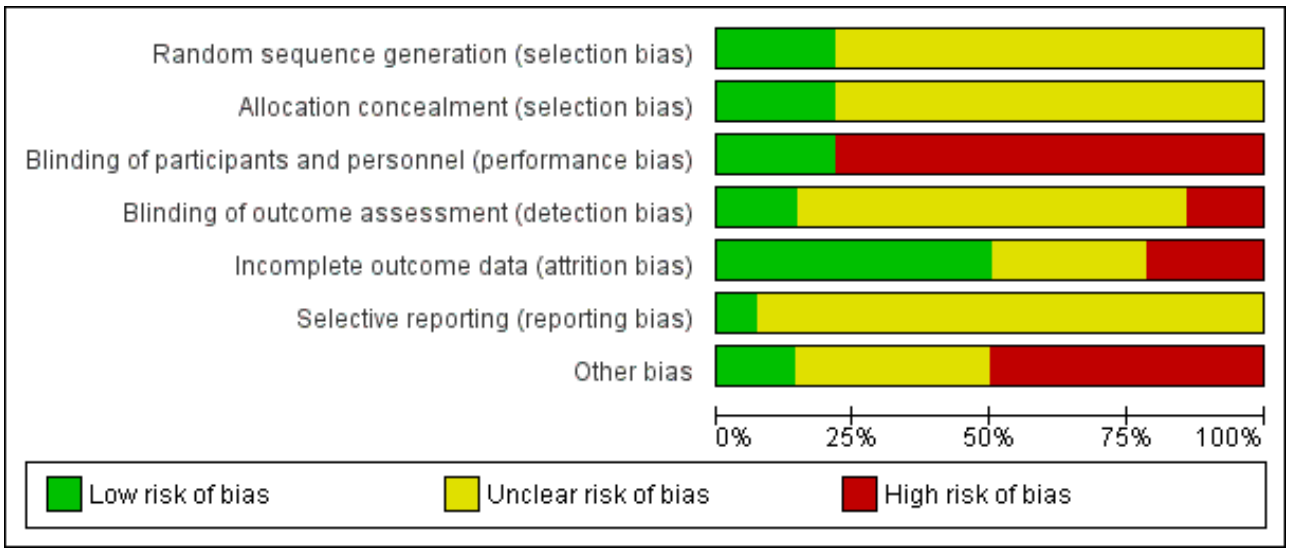


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

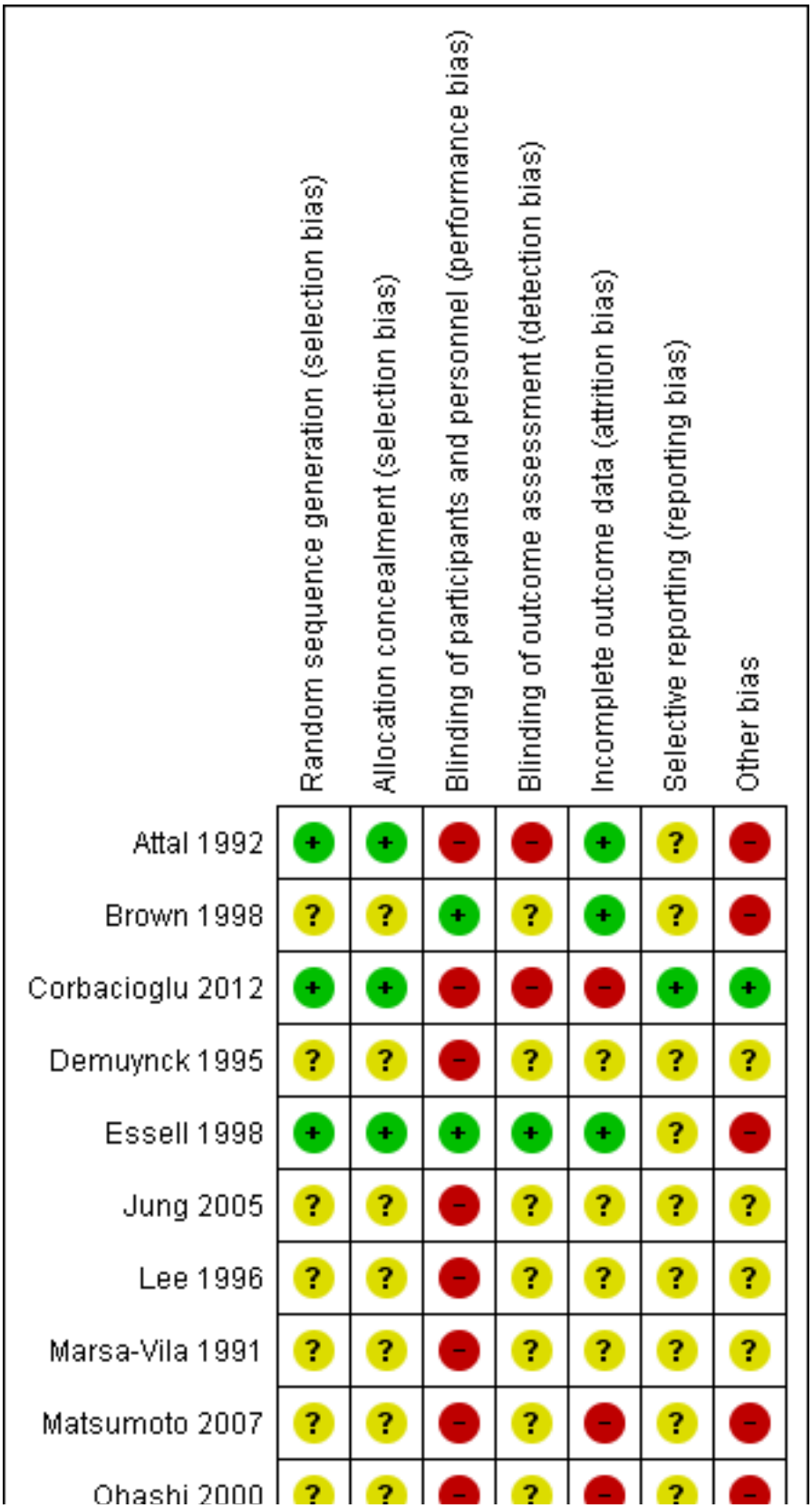
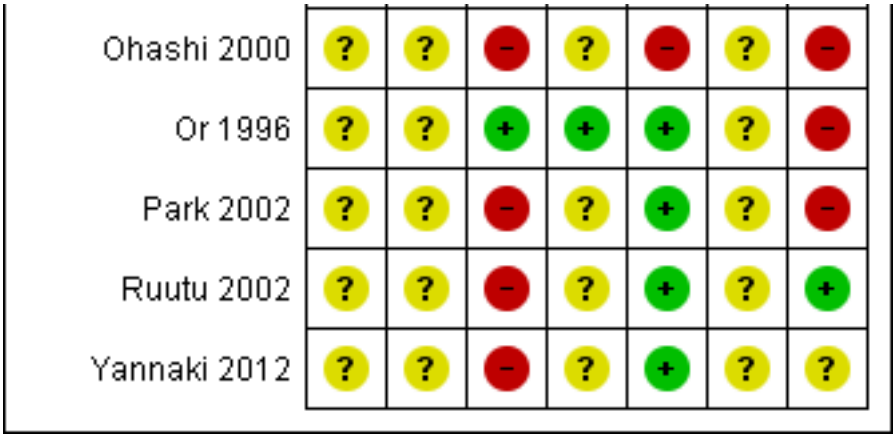


Figure 3. (Continued)



Allocation

Two studies used computer-generated random sequence for randomisation (Attal 1992; Corbacioglu 2012). The sequence was unknown to study physicians and communicated via telephone (Attal 1992) or managed by a central data manager (Corbacioglu 2012). These were considered adequate randomisation with adequate concealment and at low risk of bias. Another study used randomly assorted allocation cards stored in sealed, opaque, numbered envelops and that was also considered at low risk of bias (Essell 1998). The other studies did not describe random sequence generation or allocation concealment and were therefore considered to have unclear risk of bias (Brown 1998; Demuynck 1995; Jung 2005; Lee 1996; Marsa-Vila 1991; Matsumoto 2007; Ohashi 2000; Or 1996; Park 2002; Ruutu 2002; Yannaki 2012).

Blinding

Participants, study personnel and outcome assessors were blinded to treatment allocation in two studies (Essell 1998; Or 1996). These were considered to have low risk of bias. Participants and study personnel were also blinded in another study (Brown 1998), but it was unclear whether outcome assessors were also blinded in this study. The other studies did not attempt to blind either the participants or study personnel and therefore were considered to have high risk of bias (Attal 1992; Corbacioglu 2012; Demuynck 1995; Jung 2005; Lee 1996; Marsa-Vila 1991; Matsumoto 2007; Ohashi 2000; Park 2002; Ruutu 2002; Yannaki 2012). Outcome assessors were also not blinded in two of these studies (Attal 1992; Corbacioglu 2012). It was unclear whether outcome assessors for the remaining nine studies were blinded or not (Demuynck 1995; Jung 2005; Lee 1996; Marsa-Vila 1991; Matsumoto 2007; Ohashi 2000; Park 2002; Ruutu 2002; Yannaki 2012).

Incomplete outcome data

Outcome data were complete in five studies (Attal 1992; Brown 1998; Or 1996; Park 2002; Yannaki 2012). Dropouts occurred in only one participant in one study (Essell 1998), and one participant each in treatment and control groups in another study (Ruutu 2002). These were considered unlikely to cause attrition bias. Dropouts occurred in more than 30% of participants in one study which were considered to have high risk of bias (Corbacioglu 2012). In two other studies, the dropouts were uneven among the treatment and control groups and were considered to have high risk of bias (Matsumoto 2007; Ohashi 2000). Dropouts were not described in the remaining studies (Demuynck 1995; Jung 2005; Lee 1996; Marsa-Vila 1991) and the risk of bias was unclear.

Selective reporting

The trial protocols were not available for most included studies to judge whether there might have been selective reporting of outcomes (Attal 1992; Brown 1998; Demuynck 1995; Essell 1998; Jung 2005; Lee 1996; Marsa-Vila 1991; Matsumoto 2007; Ohashi 2000; Or 1996; Park 2002; Ruutu 2002; Yannaki 2012). These studies were therefore considered to have unclear risk of bias in this respect. One study (Corbacioglu 2012) was registered with a brief protocol available and all relevant outcomes were reported and hence considered to have low risk of bias.

Other potential sources of bias

In one study (Attal 1992), diagnostic criteria or diagnostic evaluation for hepatic VOD was not uniformly applied to all participants and therefore might cause bias. In seven studies (Attal 1992; Brown 1998; Essell 1998; Matsumoto 2007; Ohashi 2000; Or 1996; Park 2002), some of the baseline characteristics of the treatment and the control groups were not comparable and might introduce bias. In five studies (Demuynck 1995; Jung 2005; Lee 1996; Marsa-Vila 1991; Yannaki 2012), information was not available to judge whether the baseline characteristics of the treatment and the control groups were comparable. In three studies (Brown 1998; Essell 1998; Matsumoto 2007), co-interventions were different between the treatment and the control groups and this might introduce bias. In five studies (Demuynck 1995; Jung 2005; Lee 1996; Marsa-Vila 1991; Yannaki 2012), information was not available to judge whether co-intervention was comparable between the treatment and the control groups.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: Ursodeoxycholic acid versus placebo or no treatment; **Summary of findings 2** Summary of findings: Heparin versus no treatment; **Summary of findings 3** Summary of findings: Low molecular weight heparin versus placebo or no treatment; **Summary of findings 4** Summary of findings: Defibrotide versus no treatment; **Summary of findings 5** Summary of findings: Glutamine versus placebo; **Summary of findings 6** Summary of findings: Fresh frozen plasma versus no treatment; **Summary of findings 7** Summary of findings: Antithrombin III plus heparin

versus heparin alone; **Summary of findings 8** Summary of findings: Heparin versus low molecular weight heparin; **Summary of findings 9** Summary of findings: Heparin versus prostaglandin E1; **Summary of findings 10** Summary of findings: Low molecular weight heparin versus prostaglandin E1

All data presented were extracted from published reports.

Comparison 1: Ursodeoxycholic acid versus placebo or no treatment

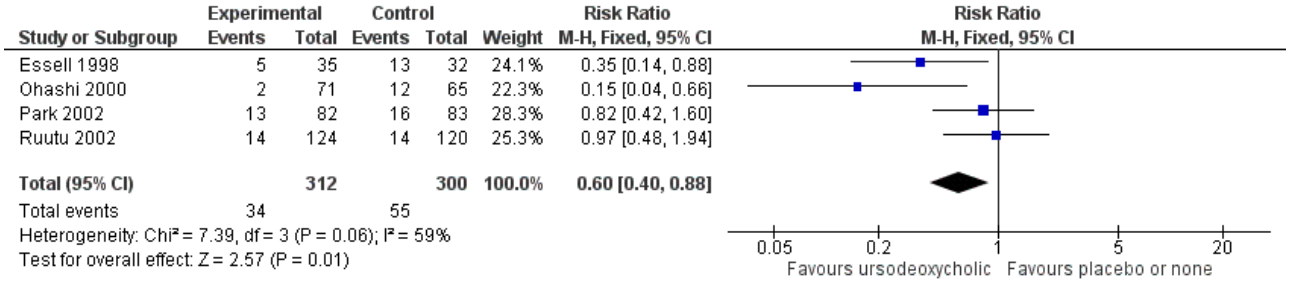
Two included trials compared ursodeoxycholic acid with placebo (Essell 1998; Ruutu 2002). One trial compared ursodeoxycholic acid with no treatment (Ohashi 2000) and one trial compared ursodeoxycholic acid plus heparin with heparin alone (Park 2002). We analysed these four trials with 612 participants together under this comparison.

Primary outcomes

Incidence of hepatic VOD

Four included studies (Essell 1998; Ohashi 2000; Park 2002; Ruutu 2002) reported this outcome. One study (Essell 1998) had one participant absent from the control group, one study (Ohashi 2000) had four participants absent from the treatment group, one study (Ruutu 2002) had one participant each in the treatment and the control group dropped out or with missing data, and they were assumed not to have developed hepatic VOD. The pooled result showed that ursodeoxycholic acid reduced the risk of development of hepatic VOD compared to control treatment (risk ratio (RR) 0.60, 95% confidence interval (CI) 0.40 to 0.88, P = 0.01, 4 trials with 612 participants) (Analysis 1.1; Figure 4). The number needed to treat for an additional beneficial outcome (NNTB) was 15 (95% CI 7 to 50). However, there was substantial heterogeneity among the studies in this outcome (I^2 = 59%; Chi^2 test P = 0.06), which might be related to differences in the participants and the treatment regimen. The missing data might also result in bias of the result. As a sensitivity analysis, a random-effects meta-analysis showed there was no evidence of a difference in the incidence of hepatic VOD between ursodeoxycholic acid and control treatment (RR 0.55, 95% CI 0.28 to 1.08, P = 0.08).

Figure 4. Forest plot of comparison: 1 Ursodeoxycholic acid versus placebo or no treatment, outcome: 1.1 Incidence of hepatic VOD.



Overall survival

The pooled result of three studies (Essell 1998; Park 2002; Ruutu 2002) showed no significant difference in overall survival between the treatment and the control groups (hazard ratio (HR) 0.83, 95% CI 0.59 to 1.18, P = 0.30, 3 of 4 trials with 77.5% of participants) (Analysis 1.2). There was moderate heterogeneity among the trials in this outcome (I^2 = 33%, Chi^2 test P = 0.22). One study (Ruutu 2002) had one participant in the treatment group who died and one participant in the control group who dropped out, and were excluded from the survival data. One study did not provide sufficient information to be included in the meta-analysis on overall survival (Ohashi 2000). However, this study commented that the survival curves did not differ significantly between the treatment and the control groups.

Secondary outcomes

All-cause mortality

All four included studies (Essell 1998; Ohashi 2000; Park 2002; Ruutu 2002) reported all-cause mortality at 100 days post-transplant. One study (Essell 1998) had one participant missing from the control group, one study (Ohashi 2000) had three participants missing from the treatment group and another study (Ruutu 2002) had one participant in the control group dropped out or with missing data, and they were assumed to be surviving. The pooled results showed that ursodeoxycholic acid reduced all-cause mortality at 100 days post-transplant compared to control treatment (RR 0.70, 95% CI 0.50 to 0.99, P = 0.04, all 4 trials with all 612 participants) (Analysis 1.3). The NNTB was 17 (95% CI 8 to 431). There was no important heterogeneity among the trials in this outcome (I^2 = 0%, Chi^2 test P = 0.46). However, the missing data might result in bias of the result.

Mortality attributable to hepatic VOD

The pooled results of all four studies (Essell 1998; Ohashi 2000; Ruutu 2002; Park 2002) showed that ursodeoxycholic acid reduced mortality attributable to hepatic VOD compared to control treatment (RR 0.27, 95% CI 0.09 to 0.87, P = 0.03, all 4 trials with all 612 participants) (Analysis 1.4). The NNTB was 34 (95% CI 16 to 220). There was no important heterogeneity among the trials in this outcome (I^2 = 0%, Chi^2 test P = 0.81). One study (Essell 1998) had one participant absent from the control group, one study (Ohashi 2000) had three participants absent from the treatment group and another study (Ruutu 2002) had one participant in the control group dropped out or with missing data, and they were assumed to be surviving. The missing data might result in bias of the result.

Quality of life

None of the four trials (Essell 1998; Ohashi 2000; Park 2002; Ruutu 2002) reported this outcome.

Frequency of adverse events

In three studies (Essell 1998; Ohashi 2000; Ruutu 2002), none of the participants in either the treatment or the control groups experienced any adverse event. Outcomes regarding one participant in the control group in one study (Essell 1998) and two participants in the treatment group in another study (Ohashi 2000) were missing and they were assumed to have no adverse events due to treatment. The missing data might result in bias of the result. In the study comparing ursodeoxycholic acid plus heparin with heparin alone (Park 2002), eight participants in the treatment group and nine participants in the control group experienced bleeding or prolonged activated partial thromboplastin time (APTT) necessitating withdrawal of treatment. There was no significant difference in the frequency of adverse events between the treatment and the control groups (RR 0.90, 95% CI 0.37 to 2.22, P = 0.82, 1 trial with all 165 participants) (Analysis 1.5).

Comparison 2: Heparin versus no treatment

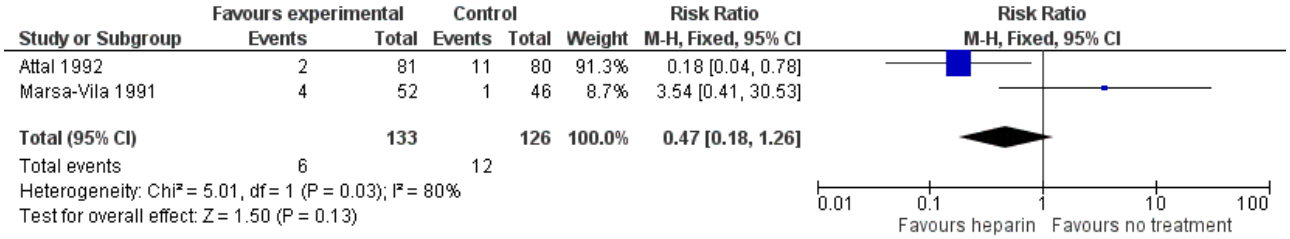
Two included studies with 259 participants compared heparin alone with no treatment (Attal 1992; Marsa-Vila 1991).

Primary outcomes

Incidence of hepatic VOD

The pooled result of the two studies (Attal 1992; Marsa-Vila 1991) showed no significant difference in the incidence of hepatic VOD between the treatment and the control groups (RR 0.47, 95% CI 0.18 to 1.26, P = 0.13, both trials with all 259 participants) (Analysis 2.1; Figure 5). There was considerable heterogeneity between the two studies (I^2 = 80%, Chi^2 test P = 0.03), which might be due to differences in participants and the type of transplant performed. As a sensitivity analysis, a random-effects meta-analysis also showed no evidence of a difference in the incidence of hepatic VOD between the treatment and the control groups (RR 0.72, 95% CI 0.04 to 13.19, P = 0.82).

Figure 5. Forest plot of comparison: 2 Heparin versus no treatment, outcome: 2.1 Incidence of hepatic VOD.



Overall survival

One study (Attal 1992) with 62.2% of all participants reported no significant difference in overall survival between the treatment group (92.6%) and the control group (88.7%) (Analysis 2.2). However, no sufficient information was available for re-analysis. The other study did not report overall survival (Marsa-Vila 1991).

Secondary outcomes

All-cause mortality

One study (Attal 1992) reported all-cause mortality at 100 days post-transplant and showed no significant difference between the treatment and the control groups (RR 0.66, 95% CI 0.25 to 1.76, P = 0.41, 1 of 2 trials with 62.2% of all participants) (Analysis 2.3). The other study did not report all-cause mortality (Marsa-Vila 1991).

Mortality attributable to hepatic VOD

One study (Attal 1992) reported mortality attributable to hepatic VOD and showed no significant difference between the treatment and the control groups (RR 0.28, 95% CI 0.06 to 1.32, P = 0.11, 1 of 2 trials with 62.2% of all participants) (Analysis 2.4). The other study did not report this outcome (Marsa-Vila 1991).

Quality of life

Neither trial (Attal 1992; Marsa-Vila 1991) reported this outcome.

Frequency of adverse events

One study reported that three participants in the treatment group experienced minor gastrointestinal bleeding (Attal 1992). None of the participants in the control group experienced this. There was no significant difference in the frequency of adverse events between the treatment and the control groups (RR 6.91, 95% CI 0.36 to 131.75, P = 0.20, 1 of 2 trials with 62.2% of all participants) (Analysis 2.5). The other study did not report adverse event (Marsa-Vila 1991).

Comparison 3: Low molecular weight heparin versus placebo or no treatment

Two studies with 106 participants compared low molecular weight heparin with placebo or no treatment, including one study comparing nadroparin with no treatment (Lee 1996) and one study comparing enoxaparin with placebo (Or 1996).

Primary outcomes

Incidence of hepatic VOD

One study (Lee 1996) reported no significant difference in the incidence of hepatic VOD between the treatment and the control groups (RR 0.27, 95% CI 0.06 to 1.18, P = 0.08, 1 of 2 trials with 42.5% of all participants) (Analysis 3.1). The other study (Or 1996) did not report the incidence of hepatic VOD, but reported frequencies of hyperbilirubinaemia, hepatic enlargement, right upper quadrant abdominal pain, ascites, and weight gain.

Overall survival

Neither study (Lee 1996; Or 1996) reported overall survival of participants.

Secondary outcomes

All-cause mortality

Neither study (Lee 1996; Or 1996) reported all-cause mortality of participants.

Mortality attributable to hepatic VOD

Neither study (Lee 1996; Or 1996) reported mortality attributable to hepatic VOD.

Quality of life

Neither study (Lee 1996; Or 1996) reported quality of life of participants.

Frequency of adverse events

One study (Or 1996) reported withdrawal of treatment because of bleeding in five participants in the treatment group and eight participants in the control group, which represented no significant difference between the two groups (RR 0.74, 95% CI 0.27 to 2.00, P = 0.55, 1 of 2 trials with 57.5% of all participants) (Analysis 3.2). The other study stated that there was no increase in haemorrhagic complications in the treatment group compared with the control group, without providing numerical data (Lee 1996).

Comparison 4: Defibrotide versus no treatment

One included study with 360 participants compared defibrotide with no treatment (Corbacioglu 2012).

Primary outcomes

Incidence of hepatic VOD

The included study (Corbacioglu 2012) revealed lower frequency of hepatic VOD in the treatment group (12.2%) compared with the control group (19.6%) but the difference was not statistically significant (RR 0.62, 95% CI 0.38 to 1.02, P = 0.06, 1 trial with all 360 participants) (Analysis 4.1). One participant in the treatment group and three participants in the control group dropped out and were assumed not to have developed VOD. This study also reported subgroup analyses for incidence of hepatic VOD. There was no statistically significant difference in the incidence of hepatic VOD between the treatment and the control groups in infants and children (RR 0.70, 95% CI 0.41 to 1.19, P = 0.19, 1 trial with 75.8% of all participants) (Analysis 4.2) or in adolescents (RR 0.35, 95% CI 0.10 to 1.22, P = 0.10, 1 trial with 23.1% of all participants) (Analysis 4.2). There was also no statistically significant difference in the incidence of hepatic VOD between the treatment and the control groups in participants with osteopetrosis (RR 0.21, 95% CI 0.03 to 1.43, P = 0.11, 1 trial with 3.6% of all participants) (Analysis 4.3) or in participants without osteopetrosis (RR 0.67, 95% CI 0.40 to 1.11, P = 0.12, 1 trial with 95.3% of all participants) (Analysis 4.3). There was no statistically significant difference in the incidence of hepatic VOD between the treatment and the control groups in participants who received allogeneic transplant (RR 0.58, 95% CI 0.32 to 1.04, P = 0.07, 1 trial with 66.4% of all participants) (Analysis 4.4) or in participants who received autologous transplant (RR 0.73, 95% CI 0.30 to 1.77, P = 0.43, 1 trial with 30% of all participants) (Analysis 4.4). There was no evidence of differences in the effects of defibrotide between different age groups (I^2 = 0%, Chi^2 test P = 0.32), between the groups with or without osteoporosis (I^2 = 21.5%, Chi^2 test P = 0.26), or between different types of transplants (I^2 = 0%, Chi^2 test P = 0.67)

Overall survival

This study (Corbacioglu 2012) showed no significant difference in the overall survival between the treatment and the control groups (HR 1.04, 95% CI 0.54 to 2.02, P = 0.90, 1 trial with 98.9% of all participants) (Analysis 4.5). One participant in the treatment group and three participants in the control group dropped out and were excluded from survival analysis. Many participants had short follow-up and only 48.1% of participants had outcome data by the end of follow-up at 180 days post-transplant. The missing data might cause bias in the result.

Secondary outcomes

All-cause mortality

There was no significant difference in all-cause mortality at 100 days post-transplant between the treatment and the control groups (RR 1.05, 95% CI 0.56 to 1.97, P = 0.89, 1 trial with all 360 participants) (Analysis 4.6). One participant in the treatment group and three participants in the control group dropped out and were assumed to be surviving.

Mortality attributable to hepatic VOD

There was no significant difference in mortality attributable to hepatic VOD between the treatment and the control groups (RR 0.40, 95% CI 0.13 to 1.24, P = 0.11, 1 trial with all 360 participants) (Analysis 4.7). One participant in the treatment group and three participants in the control group dropped out and were assumed to be surviving.

Quality of life

This study (Corbacioglu 2012) did not report quality of life of participants.

Frequency of adverse events

This study reported significantly more adverse events related to defibrotide in the treatment group compared with the control group (RR 18.79, 95% CI 1.10 to 320.45, P = 0.04, 1 trial with all 360 participants) (Analysis 4.8). There were nine adverse events related to defibrotide in the treatment group but no adverse event in the control group. Reported adverse events of participants who had received defibrotide in this study included coagulopathy, gastrointestinal disorders, haemorrhage and microangiopathy. There was no significant difference in the frequency of severe adverse events between the treatment group (three participants) and the control group (no participant) (RR 6.92, 95% CI 0.36 to 133.07, P = 0.20, 1 trial with all 360 participants) (Analysis 4.9). There was also no significant difference in the frequency of haemorrhage between the treatment group (39 participants) and the control group (37 participants) (RR 1.04, 95% CI 0.70 to 1.55, P = 0.84, 1 trial with all 360 participants) (Analysis 4.10).

Comparison 5: Glutamine versus placebo

One included study with 34 participants compared glutamine with placebo (Brown 1998).

Primary outcomes

Incidence of hepatic VOD

None of the 34 participants in this study (Brown 1998) developed hepatic VOD.

Overall survival

This study (Brown 1998) did not report overall survival of participants.

Secondary outcomes

All-cause mortality

There was no significant difference in all-cause mortality at 100 days post-transplant between the treatment and the control groups (RR 0.30, 95% CI 0.01 to 6.84, P = 0.45, 1 trial with all 34 participants) (Analysis 5.1).

Mortality attributable to hepatic VOD

There was no death attributable to VOD in this study (Brown 1998).

Quality of life

This study (Brown 1998) did not report quality of life of participants.

Frequency of adverse events

One participant who received glutamine had a sensation of abdominal fullness. None of the participants who received placebo experienced an adverse event. There was no significant difference in the frequency of adverse events between the two groups (RR 2.68, 95% CI 0.12 to 61.58, P = 0.54, 1 trial with all 34 participants) (Analysis 5.2).

Comparison 6: Fresh frozen plasma versus no treatment

One included study compared fresh frozen plasma with no treatment (Matsumoto 2007) and one study compared fresh frozen plasma plus heparin with heparin alone (Yannaki 2012). We analysed these two trials with 379 participants together.

Primary outcomes

Incidence of hepatic VOD

The pooled result of the two included studies (Matsumoto 2007; Yannaki 2012) showed no significant difference in the incidence of hepatic VOD between the treatment and the control groups (RR 0.66, 95% CI 0.20 to 2.17, P = 0.50, 2 trials of all 379 participants) (Analysis 6.1). There was moderate heterogeneity between the studies in this outcome (I^2 = 47%; Chi^2 test P = 0.17), which might be related to differences in the participants and the treatment regimen. One study (Matsumoto 2007) had one participant in the treatment group and three participants in the control group dropped out, and they were assumed not to have developed VOD. The missing data might cause bias in the result.

Overall survival

The included studies (Matsumoto 2007; Yannaki 2012) did not report overall survival of participants.

Secondary outcomes

All-cause mortality

The included studies (Matsumoto 2007; Yannaki 2012) did not report all-cause mortality of participants.

Mortality attributable to hepatic VOD

The included studies (Matsumoto 2007; Yannaki 2012) did not report mortality attributable to hepatic VOD of participants.

Quality of life

The included studies (Matsumoto 2007; Yannaki 2012) did not report quality of life of participants.

Frequency of adverse events

The included studies (Matsumoto 2007; Yannaki 2012) did not report adverse events.

Comparison 7: Antithrombin III plus heparin versus heparin alone

One included study with 30 participants compared antithrombin III plus heparin with heparin alone (Jung 2005).

Primary outcomes

Incidence of hepatic VOD

This study (Jung 2005) reported no significant difference in the incidence of hepatic VOD between the treatment and the control groups (RR 0.13, 95% CI 0.01 to 2.15, P = 0.15, 1 trial with all 30 participants) (Analysis 7.1).

Overall survival

This study (Jung 2005) did not report overall survival of participants.

Secondary outcomes

All-cause mortality

This study (Jung 2005) did not report all-cause mortality of participants.

Mortality attributable to hepatic VOD

None of the participants in this study (Jung 2005) died of hepatic VOD.

Quality of life

This study (Jung 2005) did not report quality of life of participants.

Frequency of adverse events

This study (Jung 2005) reported bleeding complications in one participant in the treatment group and four participants in the control group, which represented no significant difference between the two groups (RR 0.29, 95% CI 0.04 to 2.27, P = 0.24, 1 trial with all 30 participants) (Analysis 7.2).

Comparison 8: Heparin versus low molecular weight heparin

One included study compared heparin (47 participants) with enoxaparin (46 participants) (Demuynck 1995).

Primary outcomes

Incidence of hepatic VOD

This study (Demuynck 1995) reported no significant difference in the incidence of hepatic VOD between the two treatment groups (RR 1.96, 95% CI 0.80 to 4.77, P = 0.14, 1 trial with 93 participants) (Analysis 8.1).

Overall survival

This study (Demuynck 1995) did not report overall survival.

Secondary outcomes

All-cause mortality

This study (Demuynck 1995) did not report all-cause mortality of participants.

Mortality attributable to hepatic VOD

This study (Demuynck 1995) reported no significant difference in mortality attributable to hepatic VOD between the two treatment groups (RR 2.94, 95% CI 0.12 to 70.30, P = 0.51, 1 trial with 93 participants) (Analysis 8.2).

Quality of life

This study (Demuynck 1995) did not report quality of life of participants.

Frequency of adverse events

This study (Demuynck 1995) reported bleeding complications in six participants in the heparin group and seven participants in the enoxaparin group, which represented no significant difference between the two groups (RR 0.84, 95% CI 0.30 to 2.31, P = 0.73, 1 trial with 93 participants) (Analysis 8.3).

Comparison 9: Heparin versus prostaglandin E1

One included study compared heparin (47 participants) with prostaglandin E1 (47 participants) (Demuynck 1995).

Primary outcomes

Incidence of hepatic VOD

This study (Demuynck 1995) reported no significant difference in the incidence of hepatic VOD between the two treatment groups (RR 1.20, 95% CI 0.58 to 2.50, P = 0.63, 1 trial with 94 participants) (Analysis 9.1).

Overall survival

This study (Demuynck 1995) did not report overall survival.

Secondary outcomes

All-cause mortality

This study (Demuynck 1995) did not report all-cause mortality of participants.

Mortality attributable to hepatic VOD

This study (Demuynck 1995) reported no significant difference in mortality attributable to hepatic VOD between the two treatment groups (RR 0.50, 95% CI 0.05 to 5.33, P = 0.57, 1 trial with 94 participants) (Analysis 9.2).

Quality of life

This study (Demuynck 1995) did not report quality of life of participants.

Frequency of adverse events

This study (Demuynck 1995) reported bleeding complications in six participants who received heparin. Fourteen participants who received prostaglandin E1 experienced serious adverse events, including bleeding in two, musculoskeletal pain in six, hypotension in one, and other adverse events in five participants. There was no significant difference in the frequency of adverse events between the two groups (RR 0.43, 95% CI 0.18 to 1.02, P = 0.06, 1 trial with 94 participants) (Analysis 9.3).

Comparison 10: Low molecular weight heparin versus prostaglandin E1

One included study compared enoxaparin (46 participants) with prostaglandin E1 (47 participants) (Demuynck 1995).

Primary outcomes

Incidence of hepatic VOD

This study (Demuynck 1995) reported no significant difference in the incidence of hepatic VOD between the two treatment groups (RR 0.61, 95% CI 0.24 to 1.55, P = 0.30, 1 trial with 93 participants) (Analysis 10.1).

Overall survival

This study (Demuynck 1995) did not report overall survival.

Secondary outcomes

All-cause mortality

This study (Demuynck 1995) did not report all-cause mortality of participants.

Mortality attributable to hepatic VOD

This study (Demuynck 1995) reported no significant difference in mortality attributable to hepatic VOD between the two treatment groups (RR 0.20, 95% CI 0.01 to 4.14, P = 0.30, 1 trial with 93 participants) (Analysis 10.2).

Quality of life

This study (Demuynck 1995) did not report quality of life of participants.

Frequency of adverse events

This study reported bleeding complications in seven participants who received enoxaparin. Fourteen participants who received prostaglandin E1 experienced serious adverse events, including bleeding in two, musculoskeletal pain in six, hypotension in one, and other adverse events in five participants. There was no significant difference in the frequency of adverse events between the two groups (RR 0.51, 95% CI 0.23 to 1.15, P = 0.10, 1 trial with 93 participants) (Analysis 10.3).

Reporting bias

Since we found fewer than 10 studies for any comparison, we could not reliably assess publication bias and did not produce funnel plots for any outcome.

DISCUSSION

Summary of main results

Fourteen randomised controlled trials (RCTs) evaluated prophylactic therapies for hepatic veno-occlusive disease (VOD) in haematopoietic stem cell transplant (HSCT) recipients. Eleven trials compared active treatments with placebo or no treatment, including ursodeoxycholic acid (three trials), heparin (two trials), low molecular weight heparin (two trials), defibrotide (one trial), glutamine (one trial), fresh frozen plasma (one trial), and antithrombin III (one trial). One trial compared ursodeoxycholic

acid plus heparin with heparin alone and we meta-analysed this trial together with the other three trials on ursodeoxycholic acid. One trial compared fresh frozen plasma plus heparin with heparin alone and we meta-analysed this trial together with the other trial on fresh frozen plasma. One trial compared heparin with low molecular weight heparin and prostaglandin E1 and we conducted pair-wise comparisons.

The results showed that ursodeoxycholic acid, compared with placebo or no treatment, was associated with a reduction in the incidence of hepatic VOD, all-cause mortality, and mortality due to hepatic VOD (four RCTs; 612 participants). However, the estimates of effect size were imprecise with wide confidence intervals. There was also substantial heterogeneity in the primary outcome. Sensitivity analysis by re-analysis of the primary outcome of the incidence of hepatic VOD using a random-effects model showed no significant difference between the treatment and the control groups. All other RCTs on other prophylactic therapies failed to show efficacy in any of the outcomes considered.

In most studies, there was no evidence of a difference between the treatment and the control groups in the frequency of adverse events. One trial showed that participants who received defibrotide had more adverse events compared with the control group who did not receive defibrotide for prophylaxis. However, the estimate of the difference was grossly imprecise. Reported adverse events of defibrotide included coagulopathy, gastrointestinal disorders, haemorrhage and microangiopathy. However, there was no evidence of a difference in the frequency of severe adverse events or haemorrhage.

Overall completeness and applicability of evidence

Many different prophylactic therapies were tested in RCTs. However, most trials failed to show efficacies of these therapies when compared to placebo or no treatment, including trials on heparin, low molecular weight heparin, glutamine, fresh frozen plasma, and antithrombin III. There was no evidence of differences between Prostaglandin E1, heparin or low molecular weight heparin in any outcomes considered. In the RCT of defibrotide compared with no treatment, there was some discrepancy in the analysis and interpretation of results between the primary study report and our systematic review. The authors of the study used competing risk analysis for the cumulative incidence of hepatic VOD and found that there was a borderline statistically significant difference between the treatment and the control groups, with an absolute risk difference of 7.7% in favour of the treatment group (P = 0.0488). However, they reported statistically non-significant results when they analysed the data using the log rank test (P = 0.05). Of note is that the authors of the study excluded four randomised participants in their analyses and therefore these analyses were not genuinely intention-to-treat. Our re-analysis based on the published data assuming the four excluded participants did not develop hepatic VOD showed no evidence of a difference in the incidence of hepatic VOD between the treatment group (12.2%) and the control group (19.6%). The efficacy, if any, of defibrotide in preventing hepatic VOD appears to be modest, and the benefit was uncertain. The trial might have insufficient statistical power to detect a significant difference between the groups and further large studies are needed to clarify the efficacy of defibrotide for prophylaxis of hepatic VOD.

We found that the only agent that is possibly effective in preventing hepatic VOD in HSCT recipients is ursodeoxycholic acid, which resulted in a relative risk for hepatic VOD of 0.6, with an absolute risk difference of 7% and a number needed to treat for an additional beneficial outcome (NNTB) of 15. However, the included studies were small and the effect size estimates were imprecise. There was significant heterogeneity among the included studies in terms of participant characteristics and treatment regimens. Re-analysis of the primary outcome using a random-effects model yielded no significant difference in the incidence of hepatic VOD between the treatment and the control groups, raising further uncertainly about the efficacy of ursodeoxycholic acid. The dosing regimen of ursodeoxycholic acid and the duration of prophylaxis were variable among the trials. It remains uncertain what the optimal regimen may be, and whether ursodeoxycholic acid benefits all HSCT recipients or only certain groups . Moreover, the cost effectiveness of ursodeoxycholic acid as prophylaxis for hepatic VOD remains to be determined.

On the other hand, due to inadequate sample size in the existing trials, the failure to show clinical benefits of many prophylactic regimens may be false negative results. Therefore, the potential benefits of different prophylactic therapies in HSCT recipients cannot be entirely excluded based on the currently available evidence. Further trials of adequate sample size are needed to clarify the role of different prophylactic agents.

In addition, the included trials were of inadequate sample sizes to assess rare adverse events or to determine whether there are genuine differences in the frequency of adverse events among treatment groups.

Quality of the evidence

Apart from scarcity of RCTs and inadequate statistical power to detect differences between the treatment and the control groups, the trials included in the current review were prone to bias in different aspects. We considered that none of the included studies was at low risk of bias in all aspects assessed. In many included studies, the treatment and the control groups were not comparable at baseline, which casts doubt on the success of randomisation and increases the probability of confounding. Many included studies did not report the random sequence generation or allocation concealment which are important to minimise selection bias. Most included studies failed to blind the participants and personnel which might introduce performance bias. Some trials had significant dropouts and were prone to attrition bias. Trial protocols were not available in most trials and it was uncertain whether there was reporting bias in these RCTs.

Potential biases in the review process

There are potential biases at both the study level and the review level. The risk of bias at the study level is detailed above in the section Risk of bias in included studies. At the review level, there is possible reporting bias, as we only searched major English electronic databases and therefore non-English literature might be under-represented and missed in the review. Publication bias was also possible. However, the number of included studies was too small for formal evaluation and testing for publication bias. In addition, we only included RCTs in the review and serious or rare adverse events, or both, might have been missed.

Agreements and disagreements with other studies or reviews

There is a systematic review on the use of ursodeoxycholic acid for prophylaxis of VOD in HSCT recipients (Tay 2007). This review included four RCTs and two historically controlled studies, with a total of 824 participants. The RCTs included were the same as in our review, with similar conclusions. Ursodeoxycholic acid resulted in a lower incidence of hepatic VOD compared with placebo or no treatment (RR 0.34; 95% CI 0.17 to 0.66, P = 0.002, 3 studies). As in our findings, overall survival showed no evidence of a difference between the treatment and the control groups.

There is also a systematic review on the use of anticoagulants for prophylaxis of hepatic VOD in HSCT recipients (Imran 2006). Three RCTs and nine cohort studies with a total of 2782 participants were included in this review. The RCTs included were the same as in our review, and evaluate heparin (two RCTs) or enoxaparin (one RCT). The pooled result of all studies showed no evidence of a difference in the incidence of hepatic VOD between the treatment and the control groups (RR 0.90; 95% CI 0.62 to 1.29, P = 0.55, 12 studies). This is consistent with our review which includes RCTs only.

There is another systematic review evaluating defibrotide for prophylaxis of hepatic VOD in HSCT recipients (Zhang 2012). This review included one RCT, four cohort studies and eight case series with a total of 1230 participants. It included the same RCT (Corbacioglu 2012) as in our review. The review found that the overall mean incidence of VOD in participants who received defibrotide was lower compared with those who did not receive defibrotide (4.7% versus 13.7%, RR 0.47, 95% CI 0.31 to 0.73, P = 0.0006, 5 studies). However, the authors made similar comments to ours that the methodological weaknesses of the studies precluded making generalisable conclusions and that large RCTs were needed for further confirmation.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence of low quality that ursodeoxycholic acid might be effective in reducing the incidence of hepatic veno-occlusive disease (VOD), overall mortality and mortality due to hepatic VOD in haematopoietic stem call transplant (HSCT) recipients. However, it is uncertain whether ursodeoxycholic acid benefits all HSCT recipients or only a subset of high-risk people. The optimal regimen of ursodeoxycholic acid for prophylaxis of hepatic VOD has not been well defined. Ursodeoxycholic acid is not associated with excess adverse events compared with control groups in randomised controlled trials (RCTs). However, the small number of participants included in the RCTs precludes firm conclusion on rare adverse events. There is insufficient evidence to support the use of other prophylactic regimens, including heparin, low molecular weight heparin, defibrotide, glutamine, fresh frozen plasma, antithrombin III, or prostaglandin E1.

Implications for research

The existing trials are of small size and low methodological quality. Further high-quality RCTs of larger sample size are needed to assess the effectiveness of ursodeoxycholic acid for prophylaxis of hepatic VOD in HSCT recipients to validate its effectiveness, and to determine the group of people most likely to benefit and the optimal dosage regimen. Other therapeutic options such as defibrotide, heparin, low molecular weight heparin, glutamine, fresh frozen plasma and antithrombin III, alone or in combination with ursodeoxycholic acid also need more high-quality RCTs of larger sample size for further evaluation. Adequate random sequence generation, allocation concealment, blinding of participants, clinicians and outcome assessors are essential.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Attal 1992

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: type of graft (allogeneic or autologous) • Settings: inpatients • Study dates: January 1998 to September 1991 • Location: France
Participants	• Inclusion criteria: unpurged autologous or non-T-depleted HLA genoidentical allogeneic bone marrow transplant using standard conditioning regimen • Exclusion criteria: had lesions at risk of bleeding (e.g., recent history of peptic ulcer disease), history of deep vein thrombosis, non-standard conditioning regimen, mismatched allogeneic stem cell transplant, matched unrelated allogeneic transplant • Number of participants (intervention group : control group): 81 : 80 • Number of men (intervention group : control group): 55 : 47 • Age of participants (intervention group : control group): mean (SD) in years: 36.3 (14.4) : 35.9 (14) • Underlying diseases: Intervention group: AML (17), ALL (15), CML (18), myeloma (16), lymphoma (13), aplasia (2); Control group: AML (15), ALL (16), CML (12), myeloma (17), lymphoma (16), aplasia (4) • Previous treatments (intervention group : control group): information not available • Pre-existing liver dysfunction (intervention group : control group): AST > 40 IU/L: 10 : 7; Bilirubin > 19 micromol/L: 2 : 5

Attal 1992 *(Continued)*

- Previous history of hepatic VOD (intervention group : control group): 0 : 0
- Performance status before transplant (intervention group : control group): information not available
- Type of transplant: Intervention group: allogeneic (39), syngeneic (1), autologous (41); Control group: allogeneic (38), syngeneic (1), autologous (41)
- Donor (intervention group : control group): allogeneic (39), syngeneic (1), autologous (41); Control group: allogeneic (38), syngeneic (1), autologous (41)
- HLA disparity (intervention group : control group): information not available
- Stem cell source (intervention group : control group): all participants received bone marrow
- Stem cell manipulation (intervention group : control group): no manipulation for all participants
- Conditioning regimen: Intervention group: CY-TBI (31), MEL-TBI (14), BU-CY (25), CBV (11); Control group: CY-TBI (31), MEL-TBI (16), BU-CY (19), CBV (14)
- GVHD prophylaxis (intervention group : control group): methotrexate and cyclosporin for all participants who received allogeneic transplant

Interventions	• Intervention group (N = 81): heparin 100 units/kg/day by continuous intravenous infusion from start of conditioning till 30 days post-transplant or discharge from sterile unit, whichever occurred first • Control group (N = 80): no heparin infusion
Outcomes	• Incidence of hepatic VOD • Overall survival • Mortality attributable to hepatic VOD • Frequency of adverse event (bleeding)
Notes	• Duration of follow-up: 100 days post-transplant • Loss to follow-up (intervention group : control group): 0 : 0 • The mean interval between diagnosis and BMT appeared to be shorter in the intervention group (12.8 months) compared to the control group (16.1 months) • Funding source: information not available • Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence prepared by biostatistics department
Allocation concealment (selection bias)	Low risk	Randomisation sequence unknown to the physicians participating in the trial, treatment allocation assigned via telephone
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Physicians who assessed for presence of clinical hepatic VOD were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up was complete for all participants
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported

Attal 1992 *(Continued)*

Other bias	High risk	Diagnostic criteria or diagnostic evaluation for hepatic VOD was not uniform. The interval between diagnosis and BMT appeared to be shorter in the intervention group compared to the control group. Hence the 2 groups might not be comparable at baseline

Brown 1998

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: none • Settings: inpatients • Study dates: not reported • Location: UK
Participants	• Inclusion criteria: people undergoing stem cell transplant • Exclusion criteria: information not available • Number of participants (intervention group : control group): 18 : 16 • Number of men (intervention group : control group): 11 : 9 • Age of participants (intervention group : control group): median (range) in years: 41 (19 - 62) : 32 (16 - 55) • Underlying diseases: Intervention group: AML (2), ALL (1), CML (2), myeloma (2), non-Hodgkin lymphoma (6), Hodgkin lymphoma (5); Control group: AML (3), ALL (0), CML (2), myeloma (1), non-Hodgkin lymphoma (7), Hodgkin lymphoma (3) • Previous treatments (intervention group : control group): information not available. • Pre-existing liver dysfunction (intervention group : control group): information not available • Previous history of hepatic VOD (intervention group : control group): information not available • Performance status before transplant (intervention group : control group): information not available • Type of transplant: Intervention group: allogeneic (3), autologous (15); Control group: allogeneic (4), autologous (12) • Donor (intervention group : control group): allogeneic (3), autologous (15); Control group: allogeneic (4), autologous (12) • HLA disparity (intervention group : control group): information not available • Stem cell source: Intervention group: bone marrow (7), peripheral blood stem cell (11); Control group: bone marrow (8), peripheral blood stem cell (8) • Stem cell manipulation (intervention group : control group): information not available • Conditioning regimen: Intervention group: BEAM (10), CY-TBI (4), BU-CY (4); Control group: BEAM (9), CY-TBI (5), BU-CY (2) • GVHD prophylaxis (intervention group : control group): information not available
Interventions	• Intervention group (N = 18): glycl-L-glutamine 50 g intravenous infusion daily from the start of conditioning till discharge from the transplant unit • Control group (N = 16): placebo (isonitrogenous mixture of non-essential amino acids) 50 g intravenous infusion daily from the start of conditioning till discharge from the BMT unit
Outcomes	• Incidence of hepatic VOD • All-cause mortality • Mortality attributable to hepatic VOD • Frequency of adverse events
Notes	• Duration of follow-up: till discharge from BMT unit • Loss to follow-up (intervention group : control group): 0 : 0 • Warfarin was used in 9 participants in the intervention group but only 2 participants in the control group. 1 participant in the treatment group withdrew from the trial because of symptom of abdominal

Brown 1998 *(Continued)*

fullness. 3 other participants in the treatment group withdrew without reason given. 1 participant in the control group withdrew treatment because of problems with the supply of amino acid solution. Another participant in the control group did not complete treatment because he died soon from sepsis and graft-versus-host disease

- Funding source: information not available
- Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal of treatment occurred in some participants but their outcomes were reported
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported
Other bias	High risk	Warfarin was used more often in the intervention group compared to the control group. The participants in the intervention group also appeared to be older than those in the control group. Hence the 2 groups might not be comparable at baseline. Withdrawal of treatment occurred in 22% of participants in the intervention group and 25% of participants in the control group which might cause bias

Corbacioglu 2012

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: stratified by centre and diagnosis of osteopetrosis • Settings: inpatients • Study dates: 25 January 2006 to 29 January 2009 • Location: 28 centres in Europe
Participants	• Inclusion criteria: age below 18 years, undergoing myeloablative conditioning for allogeneic or autologous stem cell transplant, and had one or more risk factors for hepatic VOD • Exclusion criteria: pregnant women, or people who were transplanted but did not fulfil inclusion criteria • Number of participants (intervention group : control group): 181 : 179 • Number of men (intervention group : control group): 110 : 101 (gender in 1 participant in intervention group and 3 participants in control group unknown)

Corbacioglu 2012 *(Continued)*

- Age of participants (intervention group : control group): median (range) in years: 5.1 (0 - 18) : 4.6 (0 - 18) (age in 1 participant in intervention group and 3 participants in control group unknown)
- Underlying diseases: intervention group: ALL (26), AML (31), MDS (20), other leukaemia (8), neuroblastoma (34), soft tissue sarcoma (9), familial haemophagocytic lymphohistiocytosis (10), osteopetrosis (7), adrenoleukodystrophy (1), others (34), unknown (1); control group: ALL (22), AML (42), MDS (11), other leukaemia (5), neuroblastoma (33), soft tissue sarcoma (8), familial haemophagocytic lymphohistiocytosis (15), osteopetrosis (6), adrenoleukodystrophy (1), others (33), unknown (3)
- Previous treatments: intervention group: stem cell transplant (25), abdominal irradiation (9), gemtuzumab (11), unknown (1); control group: stem cell transplant (23), abdominal irradiation (8), gemtuzumab (5), unknown (3)
- Pre-existing liver dysfunction (intervention group : control group): 41 : 54 (unknown in 1 participant in intervention group and 3 participants in control group)
- Previous history of hepatic VOD (intervention group : control group): information not available
- Performance status before transplant (intervention group : control group): information not available
- Type of transplant: intervention group: allogeneic (122), autologous (53), no transplant (2), unknown (4); control group: allogeneic (117), autologous (55), no transplant (1), unknown (6)
- Donor: intervention group: matched related (35), matched unrelated (55), mismatched related (14), mismatched unrelated (18), autologous (53), no transplant (2), unknown (4); control group: matched related (25), matched unrelated (61), mismatched related (10), mismatched unrelated (21), autologous (55), no transplant (1), unknown (6)
- HLA disparity: intervention group: HLA-matched (90), HLA-mismatched (32), autologous (53), no transplant (2), unknown (4); control group: HLA-matched (86), HLA-mismatched (31), autologous (55), no transplant (1), unknown (6)
- Stem cell source: intervention group: bone marrow (79), peripheral blood stem cell (80), cord blood (16), no transplant (2), unknown (4); control group: bone marrow (81), peripheral blood stem cell (81), cord blood (10), no transplant (1), unknown (6).
- Stem cell manipulation (intervention group : control group): T-cell depletion: 6 : 4 (unknown in 1 participant in intervention group and 3 participants in control group).
- Conditioning regimen: intervention group: intravenous busulfan (80), oral busulfan (46), melphalan (126), cyclophosphamide (84), etoposide (22), fludarabine (34), treosulfan (13), TBI containing regimen (17), others (34), no transplant (2), unknown (4); control group: intravenous busulfan (81), oral busulfan (44), melphalan (114), cyclophosphamide (80), etoposide (25), fludarabine (40), treosulfan (13), TBI containing regimen (18), others (31), no transplant (1), unknown (6)
- GVHD prophylaxis: intervention group: cyclosporin (100), methotrexate (56), ATG (horse) (2), ATG (rabbit) (65), alemtuzumab (9), muromonab-CD3 (11), others (31), no GVHD prophylaxis (53), no transplant (2), unknown (4); control group: cyclosporin (104), methotrexate (65), ATG (horse) (2), ATG (rabbit) (80), alemtuzumab (5), muromonab-CD3 (7), others (28), no GVHD prophylaxis (55), no transplant (1), unknown (6)

Interventions	• Intervention group (N = 181): defibrotide 6.25 mg/kg/dose every 6 hours intravenously over 2 hours from the day of conditioning till day 30 • Control group (N = 179): no treatment
Outcomes	• Incidence of hepatic VOD • Overall survival • All-cause mortality at 100 days post-transplant • Mortality attributable to hepatic VOD • Frequency of adverse events
Notes	• Duration of follow-up: 180 days • Loss to follow-up (intervention group : control group): 10 (1 did not provide consent, 2 had adverse events, 1 transferred to another hospital, 6 unknown) : 10 (3 did not provide consent, 3 withdrew consent, 2 had adverse event, 1 had relapse, 1 transferred to another hospital). Data were available for 338 participants (93.9%) at 30 days, 269 participants (74.7%) at 100 days, and 173 participants (48.1%) at 180 days • Funding source: Gentium SpA and the European Blood and Marrow Transplantation (EBMT) Group

Corbacioglu 2012 *(Continued)*

- Declarations of interest: S Corbacioglu, J Massaro, and R D'Agostino received fees from Gentium for review activities on this report. J Massaro received payment from Gentium for writing and reviewing the report and for writing assistance. S Corbacioglu and C Peters's institutions received grants to their institutions from Gentium and K-W Sykora's institution received a grant from Medac. C Peters had given lectures and was on the speakers bureau for the Center for International Blood and Marrow Transplant Research, Amgen, and Fresenius. S Corbacioglu, J Massaro, and S Matthes-Martin had received support for travel relating to the report from Gentium. S Corbacioglu and J Massaro had received consultancy fees or honorarium from Gentium and C Peters had received such fees from Medac. M Hoyle and M Iacobelli were employees and had stock in Gentium. C Peters had received support for travel, accommodation, and meetings from Amomed and Gentium. All other authors declared that they had no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	A data manager centrally assigned eligible participants on the basis of a computer-generated randomisation sequence
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessors was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Data were available for only 48.1% of participants by the end of follow-up
Selective reporting (reporting bias)	Low risk	All outcomes in the protocol were reported
Other bias	Low risk	No other bias is evident

Demuynck 1995

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: none • Settings: inpatients • Study dates: not reported • Location: Belgium
Participants	• Inclusion criteria: people undergoing stem cell transplant • Exclusion criteria: information not available • Number of participants: PGE1 group (47); heparin group (47); enoxaparin group (46) • Number of men: information not available • Age of participants: information not available • Underlying diseases: information not available • Previous treatments: information not available

Demuynck 1995 *(Continued)*

	• Pre-existing liver dysfunction: information not available • Previous history of hepatic VOD: information not available • Performance status before transplant: information not available • Type of transplant: PGE1 group: allogeneic (14), autologous (33); heparin group: allogeneic (14), autologous (33); enoxaparin group: allogeneic (15), autologous (31) • Donor: PGE1 group: allogeneic (14), autologous (33); heparin group: allogeneic (14), autologous (33); enoxaparin group: allogeneic (15), autologous (31) • HLA disparity: information not available • Stem cell source: information not available • Stem cell manipulation: information not available • Conditioning regimen: information not available • GVHD prophylaxis (intervention group : control group): information not available
Interventions	• PGE1 group (N = 47): prostaglandin E1 500 microgram/kg/day intravenous infusion • Heparin group (N = 47): heparin 100 units/kg/day intravenous infusion • Enoxaparin group (N = 46): enoxaparin 20 mg/day subcutaneous injection
Outcomes	• Incidence of hepatic VOD • Mortality attributable to hepatic VOD • Frequency of adverse events
Notes	• Duration of follow-up: information not available. • Loss to follow-up: information not available. • Funding source: information not available. • Declarations of interest: information not available. • Information based on abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout was not described
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported

Demuynck 1995 *(Continued)*

Other bias	Unclear risk	We were not certain whether important baseline characteristics of the participants in different treatment groups were comparable or not. We were also not certain whether different treatment groups received same co-interventions

Essell 1998

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: none • Settings: inpatients • Study dates: 24 February 1992 to 4 August 1994 • Location: USA
Participants	• Inclusion criteria: allogeneic bone marrow transplant from a related donor using busulfan and cyclophosphamide as conditioning • Exclusion criteria: impaired creatinine clearance (< 50 ml/min), pregnancy, lactation, allergy to bile acids, failure to give informed consent • Number of participants (intervention group : control group): 35 : 32 • Number of men (intervention group : control group): 22 :20 • Age of participants (intervention group : control group): mean (range) in years: 38 (22 - 56) : 37 (21 - 56) • Underlying diseases: Intervention group: AML (5), ALL (3), CML (20), myeloma (3), myelodysplastic syndrome (2), myelofibrosis (0), Castleman disease (1), paroxysmal nocturnal haemoglobinuria (1); Control group: AML (9), ALL (3), CML (12), myeloma (3), myelodysplastic syndrome (1), myelofibrosis (2), Castleman disease (0), paroxysmal nocturnal haemoglobinuria (2) • Previous treatments (intervention group : control group): more than 1 cytotoxic regimen: 10 : 10 • Pre-existing liver dysfunction (intervention group : control group): elevated AST: 3 : 3 • Previous history of hepatic VOD (intervention group : control group): information not available • Performance status before transplant (intervention group : control group): mean Karnofsky performance score (range): 85 (70 - 100) : 83 (70 - 100) • Type of transplant: all participants received allogeneic bone marrow transplant from a related donor • Donor: all participants received allogeneic transplant from a related donor • HLA disparity (intervention group : control group): information not available • Stem cell source: all participants received bone marrow • Stem cell manipulation (intervention group : control group): information not available • Conditioning regimen: all participants received busulfan and cyclophosphamide • GVHD prophylaxis: all participants received methotrexate and cyclosporin
Interventions	• Intervention group (N = 35): ursodiol 300 mg twice daily orally (body weight < 90 kg), or 300 mg/600 mg twice daily (body weight > 90 kg), from before start of conditioning till 80 days post-transplant • Control group (N = 32): placebo capsules with same appearance twice daily orally from before start of conditioning till 80 days post-transplant
Outcomes	• Incidence of hepatic VOD • Overall survival • All-cause mortality at 100 days post-transplant • Mortality attributable to hepatic VOD • Frequency of adverse events
Notes	• Duration of follow-up: 1 year post-transplant • Loss to follow-up (intervention group : control group): 1 (reason not provided) : 0 • Donor-recipient blood group mismatch was less frequent in the intervention group (23%) compared to the control group (50%). Methexate was truncated less frequently in the intervention group (3%) compared to the control group (19%)

Essell 1998 *(Continued)*

- Funding source: Summit Pharmaceuticals supplied the study drug and placebo
- Declarations of interest: No financial assistance was provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Cards labelled "ursodiol" and "placebo" were placed in sealed opaque envelops and then randomised and given consecutive numbers. Randomization was done by pharmacist not involved in clinical care of patients.
Allocation concealment (selection bias)	Low risk	Allocation cards were put into sealed, opaque, numbered envelops
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was only 1 dropout (3%) in the intervention group and unlikely to have significant influence on the overall outcome
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported
Other bias	High risk	Donor-recipient blood group mismatch was less frequent in the intervention group compared to the control group. Diagnosis of CML was more frequent in the intervention group compared to the control group. Hence the 2 groups might not be comparable at baseline. Methexate was truncated less frequently in the intervention group (3%) compared to the control group (19%). The difference in this co-intervention might cause bias

Jung 2005

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: none • Settings: inpatients • Study dates: not reported • Location: Korea
Participants	• Inclusion criteria: people undergoing stem cell transplant • Exclusion criteria: information not available • Number of participants (intervention group : control group): 14 : 16 • Number of men (intervention group : control group): information not available • Age of participants (intervention group : control group): information not available • Underlying diseases: both groups: AML (9), ALL (4), acute biphenotypic leukaemia (2), CML (3), small lymphocytic leukaemia (1), myeloma (2), myelodysplastic syndrome (1), non-Hodgkin lymphoma (6), Hodgkin lymphoma (1), aplastic anaemia (1) • Previous treatments (intervention group : control group): information not available. • Pre-existing liver dysfunction (intervention group : control group): information not available

Jung 2005 *(Continued)*

	• Previous history of hepatic VOD (intervention group : control group): information not available • Performance status before transplant (intervention group : control group): information not available • Type of transplant: both groups: allogeneic (17), autologous (13) • Donor: both groups: sibling (13), unrelated (4), autologous (13) • HLA disparity (intervention group : control group): information not available • Stem cell source: both groups: bone marrow or peripheral blood stem cells (29), cord blood (1) • Stem cell manipulation (intervention group : control group): information not available • Conditioning regimen (intervention group : control group): information not available • GVHD prophylaxis (intervention group : control group): information not available
Interventions	• Intervention group (N = 14): antithrombin III 1000 units twice daily intravenously from day 1 till day 14 post-transplant and heparin 5 units/kg/hour intravenous infusion from day 1 till day 21 post-transplant or discharge after transplant • Control group (N = 16): heparin 5 units/kg/hour intravenous infusion from day 1 till day 21 post-transplant or discharge after transplant
Outcomes	• Incidence of hepatic VOD • Mortality attributable to hepatic VOD • Frequency of adverse event (bleeding)
Notes	• Duration of follow-up: information not available • Loss to follow-up (intervention group : control group): information not available • Funding source: information not available • Declarations of interest: information not available • Information based on abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout was not described.
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported.
Other bias	Unclear risk	We were not certain whether important baseline characteristics of the participants in different treatment groups were comparable or not. We were also not certain whether different treatment groups received same co-interventions.

Lee 1996

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: none • Settings: inpatients • Study dates: not reported • Location: Singapore
Participants	• Inclusion criteria: people with haematological malignancies undergoing bone marrow transplant • Exclusion criteria: information not available • Number of participants (intervention group : control group): 23 : 22 • Number of men (intervention group : control group): information not available • Age of participants (intervention group : control group): information not available • Underlying diseases: all participants had haematological malignancies • Previous treatments (intervention group : control group): information not available • Pre-existing liver dysfunction (intervention group : control group): information not available • Previous history of hepatic VOD (intervention group : control group): information not available • Performance status before transplant (intervention group : control group): information not available • Type of transplant (intervention group : control group): information not available • Donor (intervention group : control group): information not available • HLA disparity (intervention group : control group): information not available • Stem cell source: all participants received bone marrow • Stem cell manipulation (intervention group : control group): information not available • Conditioning regimen (intervention group : control group): information not available • GVHD prophylaxis (intervention group : control group): information not available
Interventions	• Intervention group (N = 23): nadroparin calcium • Control group (N = 22): no nadroparin calcium
Outcomes	• Incidence of hepatic VOD • Frequency of adverse event (bleeding)
Notes	• Duration of follow-up: information not available • Loss to follow-up (intervention group : control group): information not available • Funding source: information not available • Declarations of interest: information not available • Information based on abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor study personnel were blinded

Lee 1996 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout was not described
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported
Other bias	Unclear risk	We were not certain whether important baseline characteristics of the participants in different treatment groups were comparable or not. We were also not certain whether different treatment groups received same co-interventions

Marsa-Vila 1991

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: none • Settings: inpatients • Study dates: October 1984 to March 1989 • Location: France
Participants	• Inclusion criteria: people with haematological malignancies and solid tumours undergoing autologous bone marrow transplant • Exclusion criteria: people with an increased risk to develop hepatic VOD • Number of participants (intervention group : control group): 52 : 46 • Number of men (intervention group : control group): information not available • Age of participants (intervention group : control group): information not available • Underlying diseases: haematological malignancies or solid tumours • Previous treatments (intervention group : control group): information not available • Pre-existing liver dysfunction (intervention group : control group): information not available • Previous history of hepatic VOD (intervention group : control group): information not available • Performance status before transplant (intervention group : control group): information not available • Type of transplant: both groups: autologous bone marrow transplant • Donor: both groups: autologous • HLA disparity: both groups: autologous • Stem cell source: all participants received bone marrow • Stem cell manipulation (intervention group : control group): information not available • Conditioning regimen (intervention group : control group): information not available • GVHD prophylaxis: not applicable
Interventions	• Intervention group (N = 52): heparin 1 mg/kg/day intravenous infusion from day 0 to haematological reconstitution and discharge • Control group (N = 46): no heparin
Outcomes	• Incidence of hepatic VOD
Notes	• Duration of follow-up: information not available • Loss to follow-up (intervention group : control group): information not available • Funding source: Consejeria de Educacion of the Canary Islands Government, Spain • Declarations of interest: information not available

Marsa-Vila 1991 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout was not described
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported
Other bias	Unclear risk	We were not certain whether important baseline characteristics of the participants in different treatment groups were comparable or not. We were also not certain whether different treatment groups received same co-interventions

Matsumoto 2007

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: stratified by age to 2 groups: ≤ 18 years and > 18 years • Settings: inpatients • Study dates: April 2001 to March 2003 • Location: Japan
Participants	• Inclusion criteria: allogeneic transplant and 1 of the following: 1. intensified conditioning regimen, 2. second transplant, 3. liver dysfunction, 4. intensified chemotherapy until just before transplant • Exclusion criteria: information not available • Number of participants (intervention group : control group): 24 : 23 • Number of men (intervention group : control group): 15 : 16 (gender in 1 participant in intervention group and 3 participants in control group unknown) • Age of participants (intervention group : control group): range in years: 1 - 54 : 1 - 64 (age in 1 participant in intervention group and 3 participants in control group unknown) • Underlying diseases: intervention group: ALL (4), AML (8), MDS (4), CML (3), NHL (2), aplastic anaemia (1), Wiskott Aldrich syndrome (1), unknown (1); control group: ALL (8), AML (5), MDS (2), CML (1), NK-leukaemia (1), NHL (1); Hodgkin lymphoma (1), chronic active EBV infection (1), unknown (3) • Previous treatments (intervention group : control group): information not available • Pre-existing liver dysfunction (intervention group : control group): information not available • Previous history of hepatic VOD (intervention group : control group): information not available • Performance status before transplant (intervention group : control group): information not available • Type of transplant: both groups: allogeneic

Matsumoto 2007 *(Continued)*

	• Donor: intervention group: related (8), unrelated (15), unknown (1); control group: related (6), unrelated (14), unknown (3) • HLA disparity (intervention group : control group): information not available • Stem cell source: intervention group: bone marrow (7), peripheral blood stem cell (5), cord blood (11), unknown (1); control group: bone marrow (9), peripheral blood stem cell (5), cord blood (6), unknown (3) • Stem cell manipulation (intervention group : control group): information not available • Conditioning regimen: intervention group: myeloablative (20), non-myeloablative (3), unknown (1); control group: myeloablative (17), non-myeloablative (3), unknown (3) • GVHD prophylaxis: intervention group: cyclosporin/methotrexate (5), tacrolimus/methotrexate (7), tacrolimus/methotrexate/prednisolone (1), cyclosporin (6), tacrolimus (4), unknown (1); control group: cyclosporin/methotrexate (11), tacrolimus/methotrexate (2), cyclosporin (1), tacrolimus (5), none (1), unknown (3)
Interventions	• Intervention group (N = 24): fresh frozen plasma intravenous infusion twice weekly from conditioning till day 28. Volume: < 10 kg: 80 ml; 10 - 20 kg: 160 ml; 20 - 30 kg: 240 ml; 30 - 40 kg: 320 ml; > 40 kg: 400 ml • Control group (N = 23): no fresh frozen plasma
Outcomes	• Incidence of hepatic VOD
Notes	• Duration of follow-up: 28 days • Loss to follow-up (intervention group : control group): 1 (could not undergo transplant because of poor physical condition): 3 (could not undergo transplant because of poor physical condition) • Funding source: Ministry of Education, Culture, Sports, Science and Technology; and Ministry of Health, Labour and Welfare of Japan • Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts occurred in 4% of intervention group and 13% of control group and might cause bias
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported
Other bias	High risk	Some baseline characteristics of both groups were quite different and therefore the 2 groups might not be comparable. These included a lower proportion of ALL and higher proportion of cord blood transplant in the intervention group compared with the control group. There were more participants receiv-

Matsumoto 2007 *(Continued)*

	ing cyclosporin and fewer participants receiving combined cyclosporin and methotrexate as GVHD prophylaxis in the intervention group compared with the control group

Ohashi 2000

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: none • Settings: inpatients • Study dates: June 1996 to February 1998 • Location: Japan
Participants	• Inclusion criteria: people undergoing stem cell transplant • Exclusion criteria: information not available • Number of participants (intervention group : control group): 71 : 65 • Number of men (intervention group : control group): 40 : 30 (gender in 4 participants in intervention group unknown) • Age of participants (intervention group : control group): mean in years: 34.5 : 35.7 (age in 4 participants in intervention group unknown) • Underlying diseases: intervention group: ALL (15), acute non-lymphocytic leukaemia (23), MDS (4), CML (15), lymphoma (3), aplastic anaemia (3), others (4), unknown (4); control group: ALL (12), acute non-lymphocytic leukaemia (19), MDS (4), CML (15), lymphoma (8), aplastic anaemia (5), others (2) • Previous treatments (intervention group : control group): information not available • Pre-existing liver dysfunction (intervention group : control group): information not available • Previous history of hepatic VOD (intervention group : control group): information not available • Performance status before transplant (intervention group : control group): information not available • Type of transplant: intervention group: allogeneic (61), autologous (6), unknown (4); control group: allogeneic (56), autologous (9) • Donor: intervention group: related (39), unrelated (22), autologous (6), unknown (4); control group: related (31), unrelated (25), autologous (9) • HLA disparity: intervention group: genotypically identical (29), phenotypically identical (8), mismatched (2), unknown (4); control group: genotypically identical (27), phenotypically identical (4), mismatched (0) • Stem cell source (intervention group : control group): information not available • Stem cell manipulation (intervention group : control group): information not available • Conditioning regimen: intervention group: chemotherapy only (23), chemotherapy and TBI (34), chemotherapy and TLI (10), unknown (4); control group: chemotherapy only (18), chemotherapy and TBI (37), chemotherapy and TLI (10) • GVHD prophylaxis: intervention group: cyclosporin/methotrexate (60), tacrolimus/methotrexate (0), cyclosporin (1), unknown (4); control group: cyclosporin/methotrexate (53), tacrolimus/methotrexate (1), cyclosporin (2)
Interventions	• Intervention group (N = 71): ursodeoxycholic acid 600 mg/day orally from day -21 till day 80 • Control group (N = 65): no ursodeoxycholic acid
Outcomes	• Incidence of hepatic VOD • All-cause mortality • Mortality attributable to hepatic VOD • Frequency of adverse events
Notes	• Duration of follow-up: 24 weeks • Loss to follow-up (intervention group : control group): 4 (1 died due to regimen-related toxicity, 1 did not undergo transplant, 2 could not retrieve data sheets) : 0

Ohashi 2000 *(Continued)*

- Funding source: information not available
- Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts occurred in 6% of intervention group and none of control group and might cause bias
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported
Other bias	High risk	Some baseline characteristics of both groups were quite different and therefore the 2 groups might not be comparable. These included a higher proportion of men and lower proportion of lymphoma in the intervention group compared with the control group

Or 1996

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: stratified by type of transplant to 2 groups: allogeneic and autologous • Settings: inpatients • Study dates: August 1992 to December 1993 • Location: Israel
Participants	• Inclusion criteria: people above 15 years with malignant disease undergoing stem cell transplant • Exclusion criteria: pre-transplant platelet < $20x10^9$/L, history of major thrombotic or bleeding event, allergy to heparin • Number of participants (intervention group : control group): 28 : 33 • Number of men (intervention group : control group): 14 : 11 • Age of participants (intervention group : control group): mean (SD) in years: 40 (9.9) : 34 (10.2) • Underlying diseases: intervention group: ALL (2), AML (3), MDS (2), CML (3), CLL (1), NHL (9), Hodgkin lymphoma (2), multiple myeloma (1), solid tumour (4); control group: ALL (3), AML (6), MDS (0), CML (9), CLL (0), NHL (7), Hodgkin lymphoma (2), multiple myeloma (1), solid tumour (6) • Previous treatments (intervention group : control group): information not available • Pre-existing liver dysfunction (intervention group : control group): elevated bilirubin: 1 : 2 • Previous history of hepatic VOD (intervention group : control group): information not available

Or 1996 *(Continued)*

	• Performance status before transplant (intervention group : control group): information not available • Type of transplant: intervention group: allogeneic (8), autologous (20); control group: allogeneic (16), autologous (17) • Donor: (intervention group : control group): information not available • HLA disparity: (intervention group : control group): information not available • Stem cell source (intervention group : control group): information not available • Stem cell manipulation (intervention group : control group): information not available • Conditioning regimen: intervention group: TECAM (12), CTEM (4), ECYM and TBI (4), ECYM and TBI and TLI (5), Bu-T-CY (2), mitoxantrone and TBI (1); control group: TECAM (7), CTEM (6), ECYM and TBI (9), ECYM and TBI and TLI (6), Bu-T-CY (4), mitoxantrone and TBI (1) • GVHD prophylaxis (intervention group : control group): information not available
Interventions	• Intervention group (N = 28): enoxaparin 40 mg daily by subcutaneous injection to abdominal wall from day -1 till discharge or day 40 • Control group (N = 33): placebo (normal saline)
Outcomes	• Frequencies of hyperbilirubinaemia, hepatic enlargement, right upper quadrant abdominal pain, ascites, and weight gain • Frequency of adverse event (bleeding)
Notes	• Duration of follow-up: information not available • Loss to follow-up (intervention group : control group): 0 : 0 • Funding source: Robert A. Rosenblum Research Fund • Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no dropout
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported
Other bias	High risk	Some baseline characteristics of both groups were quite different and therefore the 2 groups might not be comparable. These included a higher proportion of men and lower proportion of chronic myeloid leukaemia and allogeneic stem cell transplant in the intervention group compared with the control group. The participants in the intervention group also had a higher mean age

Park 2002

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: none • Settings: inpatients • Study dates: February 1996 to January 2001 • Location: Korea
Participants	• Inclusion criteria: adults undergoing stem cell transplant • Exclusion criteria: life-threatening gastrointestinal or central nervous system bleeding within 2 months prior to stem cell transplant, history of allergic reaction to either heparin or ursodiol • Number of participants (intervention group : control group): 82 : 83 • Number of men (intervention group : control group): 41 : 40 • Age of participants (intervention group : control group): median in years: 39 : 38 • Underlying diseases: intervention group: acute leukaemia (23), CML (9), lymphoma (14), solid tumour (15), aplastic anaemia (9), others (12); control group: acute leukaemia (32), CML (12), lymphoma (6), solid tumour (18), aplastic anaemia (6), others (9) • Previous treatments (intervention group : control group): information not available • Pre-existing liver dysfunction (intervention group : control group): information not available • Previous history of hepatic VOD (intervention group : control group): information not available • Performance status before transplant (intervention group : control group): information not available • Type of transplant: intervention group: allogeneic (38), autologous (44); control group: allogeneic (43), autologous (40) • Donor: (intervention group : control group): information not available • HLA disparity: (intervention group : control group): information not available • Stem cell source (intervention group : control group): information not available • Stem cell manipulation (intervention group : control group): information not available • Conditioning regimen: intervention group: busulfan and cyclophosphamide (13), TBI containing regimen (27), others (42); control group: busulfan and cyclophosphamide (16), TBI containing regimen (31), others (36) • GVHD prophylaxis (intervention group : control group): information not available
Interventions	• Intervention group (N = 82): heparin 5 units/kg/hour by continuous intravenous infusion and ursodiol 300 mg every 12 hours orally from 12 - 24 hours before conditioning till discharge or day 30 • Control group (N = 83): heparin alone
Outcomes	• Incidence of hepatic VOD • Overall survival • All-cause mortality at 100 days post-transplant • Mortality attributable to hepatic VOD • Frequency of adverse event (bleeding)
Notes	• Duration of follow-up: information not available • Loss to follow-up (intervention group : control group): 0 : 0 • Funding source: information not available • Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described

Park 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no dropout
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported
Other bias	High risk	Some baseline characteristics of both groups were quite different and therefore the 2 groups might not be comparable. These included a higher proportion of lymphoma and lower proportion of acute leukaemia in the intervention group compared with the control group

Ruutu 2002

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: stratified by risk of disease (low risk or high risk), type of donor (HLA-identical sibling, other related donor, or unrelated donor), conditioning (with or without TBI), and centre (3 centres) • Settings: inpatients • Study dates: January 1996 to November 1998 • Location: Finland and Sweden
Participants	• Inclusion criteria: people undergoing allogeneic stem cell transplant • Exclusion criteria: information not available • Number of participants (intervention group : control group): 124 : 120 • Number of men (intervention group : control group): 61 : 61 (gender in 1 participant in each group unknown) • Age of participants (intervention group : control group): median (range) in years: 38 (5 - 59) : 40 (1 - 58) (age in 1 participant in each group unknown) • Underlying diseases: intervention group: ALL (26), AML (38), CML (31), CLL (2), MDS (11), NK cell leukaemia (0), multiple myeloma (2), myelofibrosis (2), essential thrombocythaemia (0), hypereosinophilic syndrome (1), NHL (2), aplastic anaemia (3), Fanconi anaemia (1), amegakaryocytic thrombocytopenia (1), chronic granulomatous disease (1), familial haemophagocytic lymphohistiocytosis (1), aspartylglucosaminuria (1), unknown (1); control group: ALL (24), AML (34), CML (37), CLL (2), MDS (12), NK cell leukaemia (1), multiple myeloma (3), myelofibrosis (1), essential thrombocythaemia (1), hypereosinophilic syndrome (0), NHL (2), aplastic anaemia (0), Fanconi anaemia (0), amegakaryocytic thrombocytopenia (0), chronic granulomatous disease (1), familial haemophagocytic lymphohistiocytosis (1), aspartylglucosaminuria (0), unknown (1) • Previous treatments (intervention group : control group): information not available • Pre-existing liver dysfunction (intervention group : control group): information not available • Previous history of hepatic VOD (intervention group : control group): information not available • Performance status before transplant (intervention group : control group): information not available

Ruutu 2002 *(Continued)*

	• Type of transplant: all participants received allogeneic transplant • Donor: intervention group: matched sibling (64), other family member (2), unrelated (57), no transplant (1); control group: matched sibling (68), other family member (0), unrelated (51), no transplant (1) • HLA disparity: (intervention group : control group): information not available • Stem cell source: intervention group: bone marrow (97), peripheral blood stem cell (26), no transplant (1); control group: bone marrow (93), peripheral blood stem cell (26), no transplant (1) • Stem cell manipulation (intervention group : control group): information not available • Conditioning regimen: intervention group: cytostatic drugs only regimen (11), TBI containing regimen (112), no transplant (1); control group: cytostatic drugs only regimen (12), TBI containing regimen (107), no transplant (1) • GVHD prophylaxis: intervention group: cyclosporin/methotrexate (63), cyclosporin/methylprednisolone (0), methotrexate/methylprednisolone (0), cyclosporin/methotrexate/methylprednisolone (57), cyclosporin/methotrexate/T-cell depletion (3), no transplant (1); control group: cyclosporin/methotrexate (60), cyclosporin/methylprednisolone (3), methotrexate/methylprednisolone (1), cyclosporin/methotrexate/methylprednisolone (55), cyclosporin/methotrexate/T-cell depletion (0), no transplant (1)
Interventions	• Intervention group (N = 124): ursodeoxycholic acid 6 mg/kg/dose twice daily orally from the day of conditioning till day 90 • Control group (N = 120): placebo
Outcomes	• Incidence of hepatic VOD • Overall survival • All-cause mortality at 100 days post-transplant • Mortality attributable to hepatic VOD • Frequency of adverse event (bleeding)
Notes	• Duration of follow-up: information not available • Loss to follow-up (intervention group : control group): 1 (died before transplantation) : 1 (cancellation of transplantation) • Funding source: information not available • Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Niether participants nor study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was only 1 dropout in each group and unlikely to have significant influence on the overall outcome

Ruutu 2002 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported
Other bias	Low risk	No other bias was identified

Yannaki 2012

Methods	• Study design: parallel-group randomised controlled trial • Stratification factor: none • Settings: inpatients • Study dates: not reported • Location: Greece
Participants	• Inclusion criteria: people who underwent haematopoietic stem cell transplant • Exclusion criteria: information not available • Number of participants (intervention group : control group): 172 : 164 • Number of men (intervention group : control group): information not available • Age of participants (both groups): median (range) in years: 36 (5 - 68) • Underlying diseases (intervention group : control group): information not available • Previous treatments (intervention group : control group): information not available • Pre-existing liver dysfunction (intervention group : control group): information not available • Previous history of hepatic VOD (intervention group : control group): information not available • Performance status before transplant (intervention group : control group): information not available • Type of transplant (both groups): autologous (152), allogeneic (184) • Donor (both groups): autologous (152), matched sibling (117), unrelated donor (61), others (6) • HLA disparity (intervention group : control group): information not available • Stem cell source (intervention group : control group): information not available • Stem cell manipulation (intervention group : control group): information not available • Conditioning regimen (both groups): busulfan (125), others (211) • GVHD prophylaxis (intervention group : control group): information not available
Interventions	• Intervention group (N = 172): fresh frozen plasma and heparin • Control group (N = 164): heparin alone
Outcomes	• Incidence of hepatic VOD
Notes	• Duration of follow-up: 100 days • Loss to follow-up (intervention group : control group): 0 : 0 • Funding source: information not available • Declarations of interest: information not available • Information based on abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described

Yannaki 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no dropout
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. It was unclear whether all pre-specified outcomes were reported
Other bias	Unclear risk	We were not certain whether important baseline characteristics of the participants in different treatment groups were comparable or not. We were also not certain whether different treatment groups received same co-interventions

ALL: acute lymphoblastic leukaemia; **AML**: acute myeloid leukaemia; **AST**: aspartate aminotransferase; **ATG**: anti-thymocyte globulin; **BEAM**: carmustine, etoposide, cytarabine, melphalan; **BMT**: bone marrow transplantation; **BU**: busulfan; **CBV**: cyclophosphamide, carmustine, etoposide; **CLL**: chronic lymphocytic leukaemia; **CML**: chronic myeloid leukaemia; **CTEM**: cyclophosphamide, thiotepa, etoposide, melphalan; **CY**: cyclophosphamide; **EBV**: Ebstein-Barr virus; **ECYM**: etoposide, cyclophosphamide, melphalan; **GVHD**: graft-versus-host disease; **HLA**: human leukocyte antigen; **MDS**: myelodysplastic syndrome; **MEL**: melphalan; **NHL**: non-Hodgkin lymphoma; **NK**: natural killer; **PGE1**: prostaglandin E1; **SD**: standard deviation; **T**: thiotepa; **TBI**: total body irradiation; **TECAM**: thiotepa, etoposide, cyclophosphamide, cytarabine, melphalan; **TLI**: total lymphoid irradiation; **VOD**: veno-occlusive disease

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Carbacioglu 2004	Trial on treatment of hepatic veno-occlusive disease and not prophylaxis

Characteristics of ongoing studies *[ordered by study ID]*

JPRN-UMIN000013455

Trial name or title	Efficacy and safety study of defibrotide (DF) for the prophylaxis of veno-occlusive disease (VOD)
Methods	Parallel-group randomised controlled trial
Participants	**Inclusion criteria:** 1. 0 - 50 years old (at informed consent) 2. Primary disease is one of the following: -malignant tumour not in remission -malignant tumour in remission. -osteopetrosis -non-malignant disease other than osteopetrosis 3. People with 1 or more following risk factors of hepatic VOD who undergo allogeneic stem cell transplantation with myeloablative conditioning regimen: -Second myeloablative transplant -Not in remission at transplant -Performance status (ECOG) of 2 or more

JPRN-UMIN000013455 *(Continued)*	-Conditioning regimen including BU-MEL or BU-CY -Liver dysfunction before stem cell transplant -Positive for anti-HCV antibody -Administration of gemtuzumab ozogamicin within 100 days before stem cell transplant -Osteopetrosis 4. Witten informed consent to participate in the study from the participant or legally acceptable representative before screening tests **Exclusion criteria:** 1. Using medication that increases risk of haemorrhage 2. Acute bleeding that is not controlled 3. Unstable haemodynamic status that require more than 1 vasopressor or decreased mean atrial pressure (MAP) 4. Complicated with viral fulminant hepatitis 5. Past history of organ transplant other than hematopoietic cell transplant 6. Complicated with grade IV GVHD 7. Women with pregnancy, breastfeeding, possible pregnancy. Men who will not consent to contraception 8. Judged as inappropriate for participating in the study by the principal or other investigator for other reasons
Interventions	• Intervention group: intravenous infusion of defibrotide 6.25 mg/kg/dose over 2 hours every 6 hours, from 1 day before starting conditioning regimen until day 30 post-transplant (for a maximum of 100 days after transplantation) • Control group: standard treatment only
Outcomes	**Primary outcome:** Incidence of hepatic VOD until day 30 post-transplant Principal or other investigator should evaluate the development of hepatic VOD according to the revised Seattle criteria. Hepatic VOD is defined as those who meet at least 2 of the following criteria by day 35 post stem cell transplant: -Total Bilirubin ≥ 2 mg/dL -Hepatomegaly -Right hypochondriac pain -Ascites -Unexplained weight gain of more than 5% from baseline **Secondary outcomes:** 1) Incidence of hepatic VOD at day 100 post-transplant 2) Incidence of hepatic VOD according to the Baltimore criteria at day 30 and day 100 post-transplant 3) Severity of hepatic VOD in people who developed VOD 4) Incidence of total, grade II-IV, and III-IV acute GVHD at day 100 post-transplant 5) Survival at day 100 and day 180 post-transplant 6) Survival at day 100 and day 180 post-transplant in people who developed hepatic VOD 7) Incidence and severity of adverse events and drug-related adverse event 8) Date of engraftment 9) Remission status of the original disease at day 30, 100, and 180 after stem cell transplant in people with malignancy
Starting date	7 March 2014
Contact information	• Name: Miwa Izutsu • Address: 3-3-2Tsukiji, Chuo-ku, Tokyo, 140-0045, Japan • Telephone: 03-6228-4835 • Email: chosei@fmu-df.jp

JPRN-UMIN000013455 *(Continued)*

Notes	

NCT00563498

Trial name or title	A randomised control study on the effects of glutamine on the clinical outcome of bone marrow transplant recipients with special reference to veno-occlusive disease and mucositis
Methods	Parallel-group randomised controlled trial
Participants	**Inclusion Criteria:** Aged above 18 years Allogeneic bone marrow transplant recipients using busulfan and cyclophosphamide as conditioning
Interventions	• Intervention group: glutamine added to parenteral nutrition • Control group: standard parenteral nutrition
Outcomes	**Primary outcomes:** Mucositis at 1 month Veno-occlusive disease at 1 month **Secondary outcomes:** Hospital stay (up to 2 months) Use of antibiotics (up to 2 months)
Starting date	July 2004
Contact information	• Name: Dr YH Leung • Address: Department of Medicine/Division of Haematology, Queen Mary Hospital, Hong Kong • Telephone: (852) 2855 3347 • Email: ayhleung@hku.hk
Notes	

BU: busulfan; **CY**: cyclophosphamide; **ECOG**: Eastern Cooperative Oncology Group; **GVHD**: graft-versus-host disease; **HCV**: hepatitis C virus; **MEL**: melphalan

DATA AND ANALYSES

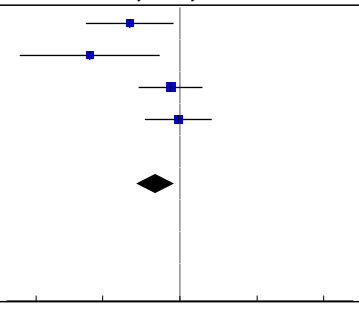
Comparison 1. Ursodeoxycholic acid versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of hepatic VOD	4	612	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.40, 0.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Overall survival	3	474	Hazard Ratio (95% CI)	0.83 [0.59, 1.18]
3 All-cause mortality at 100 days post-transplant	4	612	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.50, 0.99]
4 Mortality attributable to hepatic VOD	4	612	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.09, 0.87]
5 Frequency of adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

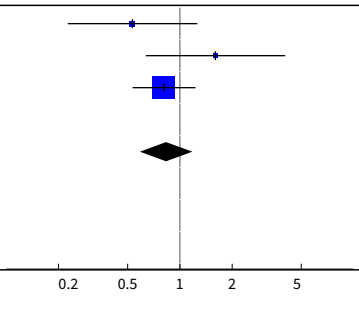
Analysis 1.1. Comparison 1 Ursodeoxycholic acid versus placebo or no treatment, Outcome 1 Incidence of hepatic VOD.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Essell 1998	5/35	13/32		24.15%	0.35[0.14,0.88]
Ohashi 2000	2/71	12/65		22.28%	0.15[0.04,0.66]
Park 2002	13/82	16/83		28.28%	0.82[0.42,1.6]
Ruutu 2002	14/124	14/120		25.3%	0.97[0.48,1.94]
Total (95% CI)	**312**	**300**		**100%**	**0.6[0.4,0.88]**
Total events: 34 (Experimental), 55 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.39, df=3(P=0.06); I^2=59.41%					
Test for overall effect: Z=2.57(P=0.01)					

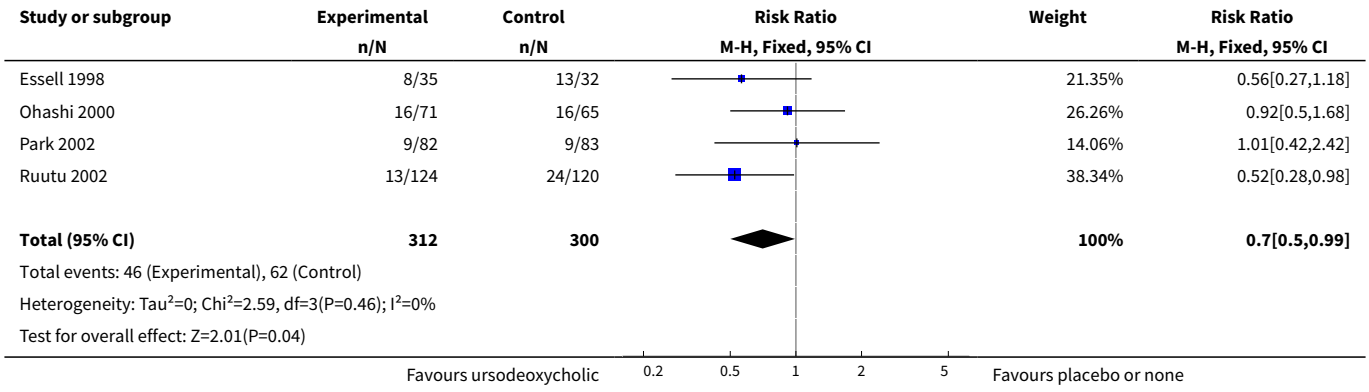


Analysis 1.2. Comparison 1 Ursodeoxycholic acid versus placebo or no treatment, Outcome 2 Overall survival.

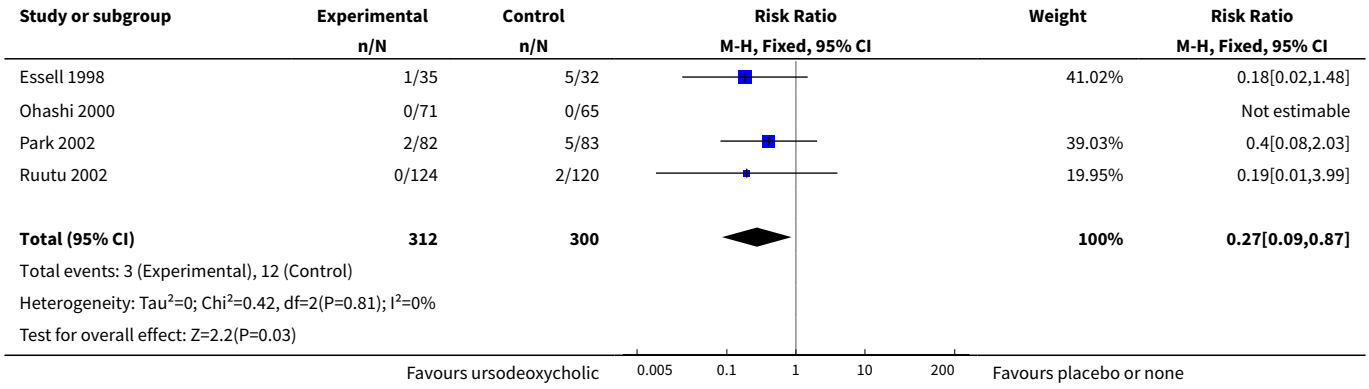
Study or subgroup	Experimental n/N	Control n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
Essell 1998	8/35	13/32		16.38%	0.53[0.23,1.26]
Park 2002	9/82	9/83		14.07%	1.6[0.64,4.04]
Ruutu 2002	36/123	53/119		69.55%	0.81[0.53,1.23]
Total (95% CI)	**240**	**234**		**100%**	**0.83[0.59,1.18]**
Total events: 53 (Experimental), 75 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.99, df=2(P=0.22); I^2=33.05%					
Test for overall effect: Z=1.04(P=0.3)					



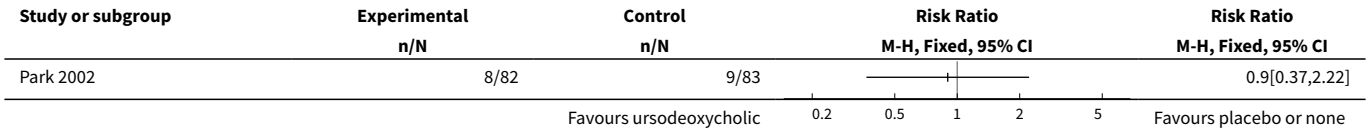
Analysis 1.3. Comparison 1 Ursodeoxycholic acid versus placebo or no treatment, Outcome 3 All-cause mortality at 100 days post-transplant.



Analysis 1.4. Comparison 1 Ursodeoxycholic acid versus placebo or no treatment, Outcome 4 Mortality attributable to hepatic VOD.



Analysis 1.5. Comparison 1 Ursodeoxycholic acid versus placebo or no treatment, Outcome 5 Frequency of adverse events.



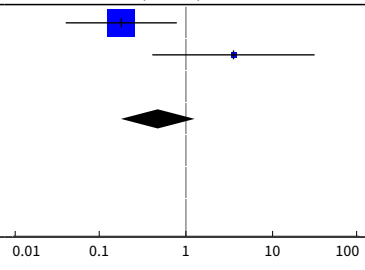
Comparison 2. Heparin versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of hepatic VOD	2	259	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.18, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Overall survival			Other data	No numeric data
3 All-cause mortality at 100 days post-transplant	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Mortality attributable to hepatic VOD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Frequency of adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Heparin versus no treatment, Outcome 1 Incidence of hepatic VOD.

Study or subgroup	Favours experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Attal 1992	2/81	11/80		91.25%	0.18[0.04,0.78]
Marsa-Vila 1991	4/52	1/46		8.75%	3.54[0.41,30.53]
Total (95% CI)	**133**	**126**		**100%**	**0.47[0.18,1.26]**
Total events: 6 (Favours experimental), 12 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.01, df=1(P=0.03); I^2=80.03%					
Test for overall effect: Z=1.5(P=0.13)					

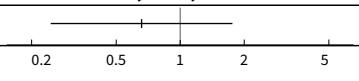


Analysis 2.2. Comparison 2 Heparin versus no treatment, Outcome 2 Overall survival.

Study	Overall survival Heparin group	No treatment group
Attal 1992	92.6%	88.7%

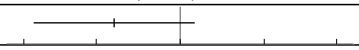
Analysis 2.3. Comparison 2 Heparin versus no treatment, Outcome 3 All-cause mortality at 100 days post-transplant.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Attal 1992	6/81	9/80		0.66[0.25,1.76]



Analysis 2.4. Comparison 2 Heparin versus no treatment, Outcome 4 Mortality attributable to hepatic VOD.

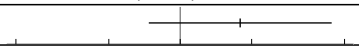
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Attal 1992	2/81	7/80		0.28[0.06,1.32]



Favours heparin — Favours no treatment

Analysis 2.5. Comparison 2 Heparin versus no treatment, Outcome 5 Frequency of adverse events.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Attal 1992	3/81	0/80		6.91[0.36,131.75]



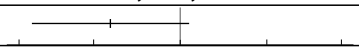
Favours heparin — Favours no treatment

Comparison 3. Low molecular weight heparin versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of hepatic VOD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Frequency of adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Low molecular weight heparin versus placebo or no treatment, Outcome 1 Incidence of hepatic VOD.

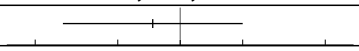
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Lee 1996	2/23	7/22		0.27[0.06,1.18]



Favours LMWH — Favours placebo or none

Analysis 3.2. Comparison 3 Low molecular weight heparin versus placebo or no treatment, Outcome 2 Frequency of adverse events.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Or 1996	5/28	8/33		0.74[0.27,2]



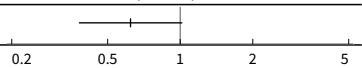
Favours LMWH — Favours placebo or none

Comparison 4. Defibrotide versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of hepatic VOD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Subgroup analyses of incidence of hepatic VOD by age groups	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Infants and children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adolescents	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Subgroup analysis for incidence of hepatic VOD by underlying diseases	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Osteopetrosis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Diseases other than osteopetrosis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Subgroup analysis of incidence of hepatic VOD by type of transplant	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Allogeneic	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Autologous	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Overall survival	1		Hazard Ratio (95% CI)	Totals not selected
6 All-cause mortality at 100 days post-transplant	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Mortality attributable to hepatic VOD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Frequency of adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Frequency of severe adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Frequency of haemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

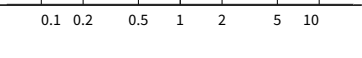
Analysis 4.1. Comparison 4 Defibrotide versus no treatment, Outcome 1 Incidence of hepatic VOD.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Corbacioglu 2012	22/181	35/179		0.62[0.38,1.02]



Analysis 4.2. Comparison 4 Defibrotide versus no treatment, Outcome 2 Subgroup analyses of incidence of hepatic VOD by age groups.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Infants and children				
Corbacioglu 2012	19/137	27/136		0.7[0.41,1.19]
4.2.2 Adolescents				
Corbacioglu 2012	3/43	8/40		0.35[0.1,1.22]



Analysis 4.3. Comparison 4 Defibrotide versus no treatment, Outcome 3 Subgroup analysis for incidence of hepatic VOD by underlying diseases.

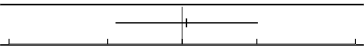
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Osteopetrosis				
Corbacioglu 2012	1/7	4/6		0.21[0.03,1.43]
4.3.2 Diseases other than osteopetrosis				
Corbacioglu 2012	21/173	31/170		0.67[0.4,1.11]

Analysis 4.4. Comparison 4 Defibrotide versus no treatment, Outcome 4 Subgroup analysis of incidence of hepatic VOD by type of transplant.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Allogeneic				
Corbacioglu 2012	15/122	25/117		0.58[0.32,1.04]
4.4.2 Autologous				
Corbacioglu 2012	7/53	10/55		0.73[0.3,1.77]

Analysis 4.5. Comparison 4 Defibrotide versus no treatment, Outcome 5 Overall survival.

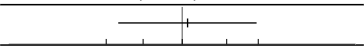
Study or subgroup	Experimental n/N	Control n/N	Hazard Ratio 95% CI	Hazard Ratio 95% CI
Corbacioglu 2012	18/180	17/176		1.04[0.54,2.02]



Favours defibrotide — Favours no treatment

Analysis 4.6. Comparison 4 Defibrotide versus no treatment, Outcome 6 All-cause mortality at 100 days post-transplant.

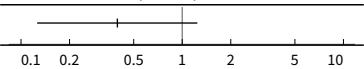
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Corbacioglu 2012	18/181	17/179		1.05[0.56,1.97]



Favours defibrotide — Favours no treatment

Analysis 4.7. Comparison 4 Defibrotide versus no treatment, Outcome 7 Mortality attributable to hepatic VOD.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Corbacioglu 2012	4/181	10/179		0.4[0.13,1.24]



Favours defibrotide — Favours no treatment

Analysis 4.8. Comparison 4 Defibrotide versus no treatment, Outcome 8 Frequency of adverse events.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Corbacioglu 2012	9/181	0/179		18.79[1.1,320.45]

Favours defibrotide — Favours no treatment

Analysis 4.9. Comparison 4 Defibrotide versus no treatment, Outcome 9 Frequency of severe adverse events.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Corbacioglu 2012	3/181	0/179		6.92[0.36,133.07]

Favours defibrotide — Favours no treatment

Analysis 4.10. Comparison 4 Defibrotide versus no treatment, Outcome 10 Frequency of haemorrhage.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Corbacioglu 2012	39/181	37/179		1.04[0.7,1.55]

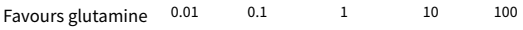
Favours defibrotide — Favours no treatment

Comparison 5. Glutamine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality at 100 days post-transplant	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Frequency of adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

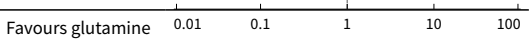
Analysis 5.1. Comparison 5 Glutamine versus placebo, Outcome 1 All-cause mortality at 100 days post-transplant.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Brown 1998	0/18	1/16		0.3[0.01,6.84]



Analysis 5.2. Comparison 5 Glutamine versus placebo, Outcome 2 Frequency of adverse events.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Brown 1998	1/18	0/16		2.68[0.12,61.58]

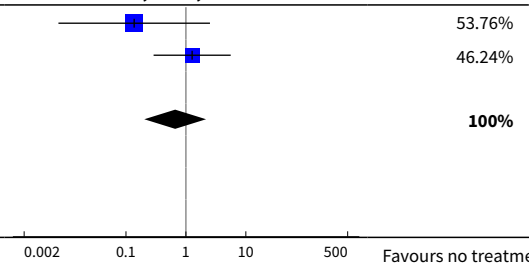


Comparison 6. Fresh frozen plasma versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of hepatic VOD	2	383	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.20, 2.17]

Analysis 6.1. Comparison 6 Fresh frozen plasma versus no treatment, Outcome 1 Incidence of hepatic VOD.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Matsumoto 2007	0/24	3/23		53.76%	0.14[0.01,2.52]
Yannaki 2012	4/172	3/164		46.24%	1.27[0.29,5.59]
Total (95% CI)	**196**	**187**		**100%**	**0.66[0.2,2.17]**
Total events: 4 (Experimental), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.87, df=1(P=0.17); I^2=46.53%					
Test for overall effect: Z=0.68(P=0.5)					

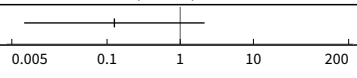


Comparison 7. Antithrombin III plus heparin versus heparin alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of hepatic VOD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Frequency of adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

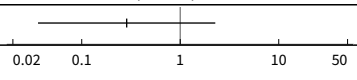
Analysis 7.1. Comparison 7 Antithrombin III plus heparin versus heparin alone, Outcome 1 Incidence of hepatic VOD.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Jung 2005	0/14	4/16		0.13[0.01,2.15]



Analysis 7.2. Comparison 7 Antithrombin III plus heparin versus heparin alone, Outcome 2 Frequency of adverse events.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Jung 2005	1/14	4/16		0.29[0.04,2.27]

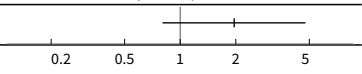


Comparison 8. Heparin versus low molecular weight heparin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of hepatic VOD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Mortality attributable to hepatic VOD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Frequency of adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

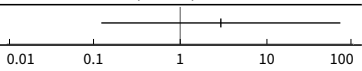
Analysis 8.1. Comparison 8 Heparin versus low molecular weight heparin, Outcome 1 Incidence of hepatic VOD.

Study or subgroup	Heparin n/N	Enoxaparin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Demuynck 1995	12/47	6/46		1.96[0.8,4.77]



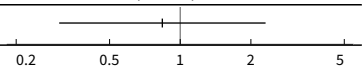
Analysis 8.2. Comparison 8 Heparin versus low molecular weight heparin, Outcome 2 Mortality attributable to hepatic VOD.

Study or subgroup	Heparin n/N	Enoxaparin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Demuynck 1995	1/47	0/46		2.94[0.12,70.3]



Analysis 8.3. Comparison 8 Heparin versus low molecular weight heparin, Outcome 3 Frequency of adverse events.

Study or subgroup	Heparin n/N	Enoxaparin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Demuynck 1995	6/47	7/46		0.84[0.3,2.31]

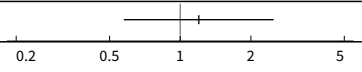


Comparison 9. Heparin versus prostaglandin E1

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of hepatic VOD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Mortality attributable to hepatic VOD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Frequency of adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 Heparin versus prostaglandin E1, Outcome 1 Incidence of hepatic VOD.

Study or subgroup	Heparin n/N	Prostaglandin E1 n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Demuynck 1995	12/47	10/47		1.2[0.58,2.5]



Analysis 9.2. Comparison 9 Heparin versus prostaglandin E1, Outcome 2 Mortality attributable to hepatic VOD.

Study or subgroup	Heparin n/N	Prostaglandin E1 n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Demuynck 1995	1/47	2/47		0.5[0.05,5.33]
		Favours heparin	0.02 0.1 1 10 50	Favours prostaglandin E1

Analysis 9.3. Comparison 9 Heparin versus prostaglandin E1, Outcome 3 Frequency of adverse events.

Study or subgroup	Heparin n/N	Prostaglandic E1 n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Demuynck 1995	6/47	14/47		0.43[0.18,1.02]
		Favours heparin	0.1 0.2 0.5 1 2 5 10	Favours prostaglandin E1

Comparison 10. Low molecular weight heparin versus prostaglandin E1

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Incidence of hepatic VOD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Mortality attributable to hepatic VOD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Frequency of adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10 Low molecular weight heparin versus prostaglandin E1, Outcome 1 Incidence of hepatic VOD.

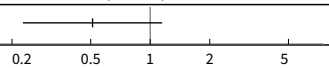
Study or subgroup	Enoxaparin n/N	Prostaglandin E1 n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Demuynck 1995	6/46	10/47		0.61[0.24,1.55]
		Favours enoxaparin	0.1 0.2 0.5 1 2 5 10	Favours prostaglandin E1

Analysis 10.2. Comparison 10 Low molecular weight heparin versus prostaglandin E1, Outcome 2 Mortality attributable to hepatic VOD.

Study or subgroup	Enoxaparin n/N	Prostaglandin E1 n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Demuynck 1995	0/46	2/47		0.2[0.01,4.14]
		Favours enoxaparin	0.005 0.1 1 10 200	Favours prostaglandin E1

Analysis 10.3. Comparison 10 Low molecular weight heparin versus prostaglandin E1, Outcome 3 Frequency of adverse events.

Study or subgroup	Enoxaparin n/N	Prostaglandin E1 n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Demuynck 1995	7/46	14/47		0.51[0.23,1.15]



APPENDICES

Appendix 1. CENTRAL search strategy

#1	Stem Cell Transplantation
#2	MeSH descriptor Hematopoietic Stem Cell Transplantation explode all trees
#3	MeSH descriptor Bone Marrow Transplantation explode all trees
#4	MeSH descriptor Peripheral Blood Stem Cell Transplantation explode all trees
#5	MeSH descriptor Cord Blood Stem Cell Transplantation explode all trees
#6	MeSH descriptor Mesenchymal Stem Cell Transplantation explode all trees
#7	(bone marrow NEAR/2 transplant*) or (bone marrow NEAR/2 graft*) or (bone marrow NEAR/2 trasplant*) or (bone marrow NEAR/2 rescue*)
#8	(stem cell* or stem-cell*)
#9	"progenitor cell*"
#10	(ASCT or ABMT or PBPC or PBSCT or PSCT or BMT or SCT or HSCT)
#11	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12	MeSH descriptor Transplantation Conditioning explode all trees
#13	myeloablat*
#14	reduced intens*
#15	(nonmyeloablat* or non-myeloablat*)
#16	(mini-tra*splant* or minitra*splant*)
#17	(#12 OR #13 OR #14 OR #15 OR #16)
#18	MeSH descriptor Transplantation, Homologous explode all trees
#19	(allograft* or allo-graft*)
#20	(allotransplant* or allo-transplant*)

(Continued)

#21	(allotrasplant* or allo-trasplant*)
#22	(allogen* or allo-gen*)
#23	(allogen* NEAR/5 transplant*) or (allogen* NEAR/5 trasplant*) or (allogen* NEAR/5 graft*) or (allogen* NEAR/5 rescue*)
#24	(allo-gen* NEAR/5 transplant*) or (allo-gen* NEAR/5 trasplant*) or (allo-gen* NEAR/5 graft*) or (allo-gen* NEAR/5 rescue*)
#25	(homograft* or homo-graft*)
#26	homolog*
#27	(homotransplant* or homo-transplant*)
#28	(homotrasplant* or homo-trasplant*)
#29	(#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)
#30	MeSH descriptor Transplantation, Autologous explode all trees
#31	(autograft* or auto-graft*)
#32	(autotransplant* or auto-transplant*)
#33	(autotra*splant* or auto-tra*splant*)
#34	(autolog* NEAR/5 (transplant* or graft* or trasplant* or rescue*))
#35	(#30 OR #31 OR #32 OR #33 OR #34)
#36	(#11 OR #17 OR #29 OR #35)
#37	MeSH descriptor Hepatic Veno-Occlusive Disease explode all trees
#38	(veno-occlusiv* or venoocclusiv*)
#39	(veno-oclusiv* or venooclusiv*)
#40	(sinusoidal* adj3 obstruct*)
#41	VOD
#42	(#37 OR #38 OR #39 OR #40 OR #41)
#43	(#36 AND #42)

Appendix 2. MEDLINE (OVID) search strategy

1	HEPATIC VENO-OCCLUSIVE DISEASE/

(Continued)

2	(veno-occlusiv$ or venoocclusiv$).tw.
3	(veno-oclusiv$ or venooclusiv$).tw.
4	(sinusoidal$ adj3 obstruct$).tw.
5	VOD.tw.
6	or/1-5
7	exp STEM CELL TRANSPLANTATION/
8	Exp HEMATOPOIETIC STEM CELL TRAN SPLANTATION/
9	Exp BONE MARROW TRANSPLANTATION/
10	PERIPHERAL BLOOD STEM CELL TRANSPLANTATION/
11	CORD BLOOD STEM CELL TRANSPL ANTATION/
12	MESENCHYMAL STEM CELL TRANSP LANTATION/
13	(bone marrow adj2 (transplant$ or graft$ or trasplant$ or rescue$)).tw.
14	(stem cell$ or stem-cell$).tw.
15	"progenitor cell$".tw.
16	(ASCT or ABMT or PBPC or PBSCT or PSCT or BMT or SCT or HSCT).tw.
17	or/7-16
18	MYELOABLATIVE CONDITIONING/ or NONMYELOABLATIVE CONDITIONING/ or REDUCED INTENSITY CONDITIONING/
19	myeloablat$.tw.
20	reduced intens$.tw.
21	(nonmyeloablat$ or non-myeloablat$).tw.
22	(mini-tra?splant$ or minitra?splant$).tw.
23	or/18-22
24	exp ALLOTRANSPLANTATION/
25	(allograft$ or allo-graft$).tw.
26	(allotransplant$ or allo-transplant$).tw.
27	(allotrasplant$ or allo-trasplant$).tw.
28	(allogen$ or allo-gen$).tw.
29	((allogen$ or allo-gen$) adj5 (transplant$ or trasplant$ or graft$ or rescue$)).tw.

(Continued)

30	(homograft$ or homo-graft$).tw.
31	homolog*.tw.
32	(homotransplant$ or homo-transplant$).tw.
33	(homotrasplant$ or homo-trasplant$).tw.
34	or/24-33
35	AUTOTRANSPLANTATION/
36	(autograft$ or auto-graft$).tw.
37	(autotransplant$ or auto-transplant$).tw.
38	(autotra?splant$ or auto-tra?splant$).tw.
39	(autolog$ adj5 (transplant$ or graft$ or trasplant$ or rescue$)).tw.
40	or/35-39
41	17 or 23 or 34 or 40
42	6 and 41
43	randomised controlled trial.pt.
44	controlled clinical trial.pt.
45	randomized.ab.
46	placebo.ab.
47	drug therapy.fs.
48	randomly.ab.
49	trial.ab.
50	groups.ab.
51	or/43-50
52	humans.sh.
53	51 and 52
54	42 and 53

Appendix 3. EMBASE (OVID) search strategy

1	LIVER VENOOCCLUSIVE DISEASE/
2	(veno-occlusiv$ or venoocclusiv$).tw.
3	(veno-oclusiv$ or venooclusiv$).tw.
4	(sinusoidal$ adj3 obstruct$).tw.
5	VOD.tw.
6	or/1-5
7	exp STEM CELL TRANSPLANTATION/
8	Exp HEMATOPOIETIC STEM CELL TRAN SPLANTATION/
9	Exp BONE MARROW TRANSPLANTATION/
10	PERIPHERAL BLOOD STEM CELL TRANSPLANTATION/
11	CORD BLOOD STEM CELL TRANSPL ANTATION/
12	MESENCHYMAL STEM CELL TRANSP LANTATION/
13	(bone marrow adj2 (transplant$ or graft$ or trasplant$ or rescue$)).tw.
14	(stem cell$ or stem-cell$).tw.
15	"progenitor cell$".tw.
16	(ASCT or ABMT or PBPC or PBSCT or PSCT or BMT or SCT or HSCT).tw.
17	or/7-16
18	(MYELOABLATIVE CONDITIONING or NONMYELOABLATIVE CONDITIONING or REDUCED INTENSITY CONDITIONING).sh,hw.
19	myeloablat$.tw.
20	reduced intens$.tw.
21	(nonmyeloablat$ or non-myeloablat$).tw.
22	(mini-tra?splant$ or minitra?splant$).tw.
23	or/18-22
24	exp ALLOTRANSPLANTATION/
25	(allograft$ or allo-graft$).tw.
26	(allotransplant$ or allo-transplant$).tw.
27	(allotrasplant$ or allo-trasplant$).tw.
28	(allogen$ or allo-gen$).tw.

(Continued)

29	((allogen$ or allo-gen$) adj5 (transplant$ or trasplant$ or graft$ or rescue$)).tw.
30	(homograft$ or homo-graft$).tw.
31	homolog*.tw.
32	(homotransplant$ or homo-transplant$).tw.
33	(homotrasplant$ or homo-trasplant$).tw.
34	or/24-33
35	AUTOTRANSPLANTATION/
36	(autograft$ or auto-graft$).tw.
37	(autotransplant$ or auto-transplant$).tw.
38	(autotra?splant$ or auto-tra?splant$).tw.
39	(autolog$ adj5 (transplant$ or graft$ or trasplant$ or rescue$)).tw.
40	or/35-39
41	17 or 23 or 34 or 40
42	6 and 41
43	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
44	RETRACTED ARTICLE/
45	or/43-44
46	(animal$ not human$).sh,hw.
47	(book or conference paper or editorial or letter or review).pt. not exp randomised controlled trial/
48	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomised controlled trial/
49	45 not (46 or 47 or 48)
50	42 and 49

CONTRIBUTIONS OF AUTHORS

DKL Cheuk: conceiving of the review, protocol development, searching for trials, selection of studies, quality assessment of trials, data extraction, data input, data analyses, development of final review, corresponding author.

AKS Chiang: review of the protocol, selection of studies, quality assessment of trials, data extraction, data input, data analyses, development of final review.

SY Ha: review of the protocol and development of final review.

GCF Chan: review of the protocol and development of final review.

DECLARATIONS OF INTEREST

Daniel KL Cheuk:None known

Alan KS Chiang:None known

Shau Yin Ha:None known

Godfrey CF Chan:None known

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Internal sources

- The University of Hong Kong, Hong Kong.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not produce a funnel plot because of insufficient number of studies identified. We did not conduct sensitivity analyses because all studies had high risk of bias. We assessed subgroup differences by examining the I^2 statistic and performing Chi^2 test for heterogeneity across subgroup results. For outcomes with substantial heterogeneity, we performed random-effects meta-analyses as a sensitivity analysis. We did not impute missing data, except for mortality and incidence of hepatic VOD data, but assumed that participants had not died or developed VOD if their data were missing.

INDEX TERMS

Medical Subject Headings (MeSH)

Antithrombin III [therapeutic use]; Cause of Death; Cholagogues and Choleretics [*therapeutic use]; Glutamine [therapeutic use]; Hematopoietic Stem Cell Transplantation [*adverse effects]; Heparin, Low-Molecular-Weight [therapeutic use]; Hepatic Veno-Occlusive Disease [mortality] [*prevention & control]; Plasma; Polydeoxyribonucleotides [therapeutic use]; Randomized Controlled Trials as Topic; Ursodeoxycholic Acid [*therapeutic use]

MeSH check words

Female; Humans; Male