The SAFE Study
(Saline v Albumin Fluid Evaluation)

Australian and New Zealand Intensive Care Society
Clinical Trials Group,
Australian Red Cross Blood Service
The George Institute for International Health, University of Sydney
SAFE (Saline v Albumin Fluid Evaluation) Study Initiated in Australia and New Zealand

- To compare the effects of two resuscitation fluids (4% human albumin or saline) on 28-day all-cause mortality in ICU patients requiring intravascular volume resuscitation
- Hypothesis: no difference in mortality at 28 days
Study Design and Sample Size

- Multicenter, randomized, double-blind controlled trial
- To compare the effects of two resuscitation fluids (4% human albumin or saline) on 28-day all-cause mortality in ICU patients requiring intravascular volume resuscitation
- 7,000 patients, 16 ICUs in Australia and New Zealand
- 90% power to detect 3% difference in absolute mortality from an estimated baseline mortality of 15%
SAFE Study: Participating Institutions

1. Alfred Hospital, Melbourne, Victoria - Julie Charlton, James Cooper, Andrew Davies, Catherine Harry, Lisa Higgins, Katherine Moulden, Shirley Vallance.
2. Auckland Hospital, Auckland (NZ) - Janine Chadderton, Lynette Newby, Colin McArthur
4. Fremantle Hospital, Fremantle, Western Australia - David Blythe, Annamaria Palermo.
5. John Hunter Hospital, Newcastle, NSW – Rosemary Carroll, Brett McFadyen, Peter Saul.
6. Middlemore Hospital, Auckland (NZ) - Jane Clarke, Juliet Powell, Anthony Williams, Judi Tai.
8. Princess Alexandra Hospital, Brisbane, Queensland - Lisa Bradley, Christopher Joyce, Theresa Kelly, Anthony Limpus, Robyn Moore.
9. Royal Adelaide Hospital, South Australia - Marianne Chapman, Stephanie Creed, Sandra Kaplan, Justine Rivett.
10. Royal Darwin Hospital, Northern Territory - Dianne Stephens, Jane Thomas.
11. Royal Hobart Hospital, Tasmania - Anthony Bell, Kathy Marsden, Andrew Turner.
12. Royal Melbourne Hospital, Victoria - Catherine Boyce, John Cade, Belinda Howe, Jeffrey Presneill, Megan Robertson.
14. Royal Prince Alfred Hospital, Sydney, NSW – Catherine Powell, Dorrilyn Rajbhandari, Clive Woolfe.
15. St George Hospital, Sydney, NSW - Kathryn Girling, Marie Hodgetts, Alina Jovanovska, John Myburgh.
16. Western Hospital, Melbourne, Victoria - Craig French, Lorraine Little.

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Pre-defined subgroups

- Trauma
- Severe Sepsis
- Acute Respiratory Distress Syndrome
Main Inclusion Criteria

- Needs intravascular fluid resuscitation in ICU
- Treating doctor has substantial uncertainty over best fluid to give
- Informed consent if competent, otherwise delayed consent
Main Exclusion Criteria

- Age less than 18 years
- Burns
- Cardiac surgery
- Liver transplantation
- Allergy or religious objection to albumin
- Moribund
The SAFE Study

A multi-centre double blind randomised controlled trial of the effects on intravenous volume replacement with albumin compared to saline in critically ill patients

About the study
(PDF)

Contact Details
(PDF)

A joint initiative of:
Australian & New Zealand Intensive Care Society Clinical Trials Group
Institute for International Health, University of Sydney
Australian Red Cross Blood Service

Registered Users

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Last updated: 21 April 2002

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Funding bodies

- Auckland District Health Board, New Zealand
- Australian Commonwealth Department of Health and Aged Care
- Australian National Health and Medical Research Council
- CSL Limited, Melbourne (Australia)
- Health Department of Western Australia
- Health Research Council of New Zealand
- Middlemore Hospital, New Zealand
- New South Wales Health Department (Australia)
- Northern Territory Health Services (Australia)
- Queensland Health Services Department (Australia)
- Royal Hobart Hospital, Tasmania (Australia)
- South Australian Department of Human Services
- Victorian Department of Human Services (Australia)
Study Treatments:

4% albumin (ALBUMEX®) or saline

Manufactured by CSL Limited, Melbourne, Australia.
Study Design

- Blinding – formally tested prior to study
Study Design

• Packaging
Study Design

- Distribution
Study Design

- Administration
**Fluid administration**

- The treating clinicians decided the amount and rate of fluid administration according to each patient’s clinical status and response to treatment.
- The allocated study treatment was used for all fluid resuscitation in the ICU until death or discharge or until 28 days following randomization.
- Administration of intravenous fluids outside the ICU was not controlled.
- All other aspects of patient care were performed at the discretion of treating clinicians.
Concomitant treatments

- All other aspects of patient care were performed at the discretion of treating clinicians.
Outcome measures

- Primary outcome: death from all causes at 28 days.

- Secondary outcomes:
  - survival during the first 28 days
  - proportion of patients with new organ failures
  - duration of mechanical ventilation
  - duration of renal replacement therapy
  - duration of ICU and hospital stay
Interim analyses

- Two pre-planned interim analyses
  - independent statistician
  - following recruitment of 2333 (33%) and 4666 (67%) patients
  - reviewed by the independent data monitoring committee (Chair – Prof. Sir Richard Peto)
SAFE Study: Actual v Target Recruitment

Week of Study

Number Recruited

Actual Recruitment
Target Recruitment
Number randomized = 7000

Randomized twice in 28 day period = 3, (albumin =2, saline = 1)

Allocated to albumin = 3497 (100%)

Lost to follow-up = 24 (0.7%)
Refused or withdrawn consent = 20 (0.6%)
Randomization failure assumed = 4 (0.1%)

Analyzed = 3473 (99.3%)

Allocated to saline = 3500 (100%)

Lost to follow-up = 40 (1.1%)
Refused or withdrawn consent = 37 (1.0%)
Randomization failure assumed = 3 (0.1%)

Analyzed = 3460 (98.9%)

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### Baseline Characteristic

<table>
<thead>
<tr>
<th></th>
<th>Albumin</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years - mean ± SD</td>
<td>58.6 ± 19.1</td>
<td>58.5 ± 18.7</td>
</tr>
<tr>
<td>Female gender – N (%)</td>
<td>1424 (40.7)</td>
<td>1376 (39.3)</td>
</tr>
<tr>
<td>Reason for admission to ICU – N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>1,473 (42.9)</td>
<td>1,465 (42.7)</td>
</tr>
<tr>
<td>Medical</td>
<td>1,955 (57.1)</td>
<td>1,958 (57.3)</td>
</tr>
<tr>
<td>Pre-defined sub-groups – N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>597 (17.4)</td>
<td>590 (17.2)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>603 (18.1)</td>
<td>615 (18.4)</td>
</tr>
<tr>
<td>ARDS</td>
<td>61 (1.8)</td>
<td>66 (1.9)</td>
</tr>
<tr>
<td>APACHE II score - mean ± SD</td>
<td>18.7 ± 7.9</td>
<td>19.0 ± 8.0</td>
</tr>
</tbody>
</table>
### Baseline Characteristic

<table>
<thead>
<tr>
<th>Physiological variable</th>
<th>Albumin</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats per minute)</td>
<td>91.4 ± 23.5</td>
<td>92.3 ± 23.5</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>77.8 ± 16.4</td>
<td>78.2 ± 16.3</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
<td>9.0 ± 4.7</td>
<td>8.6 ± 4.6</td>
</tr>
<tr>
<td>Urine output (mL last hour)</td>
<td>89.7 ± 132.4</td>
<td>95.0 ± 161.4</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>27.4 ± 7.8</td>
<td>27.7 ± 7.9</td>
</tr>
</tbody>
</table>

### Treatment at baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Albumin</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receiving mechanical ventilation – N (%)</td>
<td>2186 (63.8)</td>
<td>2217 (64.8)</td>
</tr>
<tr>
<td>Receiving renal replacement therapy – N (%)</td>
<td>45 (1.3)</td>
<td>41 (1.2)</td>
</tr>
<tr>
<td>Received albumin in prior 72 hours – N (%)</td>
<td>127 (3.7)</td>
<td>135 (3.9)</td>
</tr>
</tbody>
</table>
*Mean volume of study fluid administered (mL per patient per day)*

![Bar chart showing the mean volume of study fluid administered for different days, with bars for Albumin and Saline.](image)

Ratio of albumin to saline for first four days = 1:1.4
(Mean difference per randomized patient for first four days 749 mL)
Mean Volume of Packed Red Blood Cells Administered (mL per patient per day)

Mean difference per randomized patient first four days = 71.0 mL
Mean arterial pressure

Heart rate

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Central venous pressure

![Central venous pressure graph](image)

Day | ALBUMIN | SALINE | DIFFERENCE |
---|---------|--------|------------|
1  | 11.2    | 10.0   | 1.2        |
2  | 11.6    | 10.4   | 1.2        |
3  | 11.4    | 10.7   | 0.77       |
4  | 11.1    | 10.5   | 0.60
Serum albumin

Serum albumin (g/L)

Day

Baseline 1 2 3 4

* * * *

* p<0.001

Albumin
Saline

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Primary Outcome - all patients

- Albumin  – 726 deaths in 3473 patients (20.9%)
- Saline    – 729 deaths in 3460 patients (21.1%)

- Relative risk 0.99, (0.91 - 1.09)
- P = 0.87
Kaplan-Meier estimates for probability of survival; P=0.96
Secondary outcomes – all patients

- Days of mechanical ventilation
  - Albumin $4.5 \pm 6.1$
  - Saline $4.3 \pm 5.7$ \( P = 0.74 \)

- Days renal replacement therapy
  - Albumin $0.48 \pm 2.28$
  - Saline $0.39 \pm 2.0$ \( P = 0.41 \)
### Secondary outcomes – all patients

<table>
<thead>
<tr>
<th>New Organ Failures</th>
<th>Albumin</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1,397 (52.7%)</td>
<td>1,424 (53.3%)</td>
</tr>
<tr>
<td>1</td>
<td>795 (30.0%)</td>
<td>796 (29.8%)</td>
</tr>
<tr>
<td>2</td>
<td>369 (13.9%)</td>
<td>361 (13.5%)</td>
</tr>
<tr>
<td>3</td>
<td>68 (2.6%)</td>
<td>75 (2.8%)</td>
</tr>
<tr>
<td>4</td>
<td>18 (0.7%)</td>
<td>17 (0.6%)</td>
</tr>
<tr>
<td>5</td>
<td>2 (0.1%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

P = 0.85
Relative risk of death for all patients and subgroups.

<table>
<thead>
<tr>
<th></th>
<th>Deaths / Total</th>
<th>Favors albumin</th>
<th>Favors saline</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>726 / 3473</td>
<td>729 / 3460</td>
<td>0.99 (0.91, 1.09)</td>
<td></td>
</tr>
<tr>
<td>With trauma</td>
<td>81 / 596</td>
<td>59 / 590</td>
<td>1.36 (0.99, 1.86)</td>
<td></td>
</tr>
<tr>
<td>Without trauma</td>
<td>641 / 2831</td>
<td>666 / 2830</td>
<td>0.96 (0.88, 1.06)</td>
<td></td>
</tr>
<tr>
<td>With severe sepsis</td>
<td>185 / 603</td>
<td>217 / 615</td>
<td>0.87 (0.74, 1.02)</td>
<td></td>
</tr>
<tr>
<td>Without severe sepsis</td>
<td>518 / 2734</td>
<td>492 / 2720</td>
<td>1.05 (0.94, 1.17)</td>
<td></td>
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<tr>
<td>With ARDS</td>
<td>24 / 61</td>
<td>28 / 66</td>
<td>0.93 (0.61, 1.41)</td>
<td></td>
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<tr>
<td>Without ARDS</td>
<td>697 / 3365</td>
<td>697 / 3354</td>
<td>1.00 (0.91, 1.01)</td>
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Comparison of Treatment Effects
With trauma vs. without trauma

Relative risk of death for patients assigned albumin versus saline:
With trauma 1.36, without trauma 0.96
P=0.04 (Test for common relative risk)
Mortality in patients with trauma, with and without brain injury.

- Trauma:
  - Without trauma: n=81, n=59
  - p=0.055

- Trauma with TBI:
  - n=59
  - n=38
  - p=0.009

- Trauma without TBI:
  - n=22
  - n=21
Trauma with and without brain injury (TBI)

### Mortality (%)

#### Trauma
- **With TBI**: 81/596
- **Without TBI**: 641/2831
- **P-value**: 0.055

#### Trauma without TBI
- **With Albumin**: 59/240
- **With Saline**: 38/252
- **P-value**: 0.009

#### Trauma with TBI
- **With Albumin**: 22/356
- **With Saline**: 21/338
SAFE TBI: Aim

- To better define baseline balance of factors known to influence outcome in patients with TBI
- To quantify outcomes in terms relevant to TBI
SAFE TBI - Outcome data

Vital status

6 months and 12 months

Functional status

24 month extended Glasgow Outcome Score

Completion

Follow up – June 2005

Analysis – December 2005
Comparison of Treatment Effects
With vs. without severe sepsis

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Relative risk of death for patients assigned albumin versus saline:
With severe sepsis 0.87, without severe sepsis 1.05
P=0.06 (Test for common relative risk)
Mortality in patients with and without severe sepsis.
Study Conclusions

• In heterogeneous population of ICU patients, albumin and saline are clinically equivalent treatments.

• Use of either results in:
  • Similar mortality
  • Similar time to death in those who die
  • Similar use of mechanical ventilation and renal replacement therapy
  • Similar incidence of new organ failures
  • Similar ICU and hospital length of stay
Further analyses

- By baseline albumin
- Sepsis cohort
- Trauma and TBI
- Patterns of organ dysfunction
THANK YOU