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Hemodynamic optimization in severe trauma: a systematic review and meta-analysis

Otimização hemodinâmica em trauma grave: uma revisão sistemática e metanálise

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ABSTRACT

Objective: Severe trauma can be associated with significant hemorrhagic shock and impaired organ perfusion. We hypothesized that goal-directed therapy would confer morbidity and mortality benefits in major trauma.

Methods: The MedLine, Embase and Cochrane Controlled Clinical Trials Register databases were systematically searched for randomized, controlled trials of goal-directed therapy in severe trauma patients. Mortality was the primary outcome of this review. Secondary outcomes included complication rates, length of hospital and intensive care unit stay, and the volume of fluid and blood administered. Meta-analysis was performed using RevMan software, and the data presented are as odds ratios for dichotomous outcomes and as mean differences (MDs) and standard MDs for continuous outcomes.

Results: Four randomized, controlled trials including 419 patients were analyzed. Mortality risk was significantly reduced in goal-directed therapy-treated patients, compared to the control group (OR=0.56, 95%CI: 0.34-0.92). Intensive care (MD: 3.7 days 95%CI: 1.06-6.5) and hospital length of stay (MD: 3.5 days, 95%CI: 2.75-4.25) were significantly shorter in the protocol group patients. There were no differences in reported total fluid volume or blood transfusions administered. Heterogeneity in reporting among the studies prevented quantitative analysis of complications.

Conclusion: Following severe trauma, early goal-directed therapy was associated with lower mortality and shorter durations of intensive care unit and hospital stays. The findings of this analysis should be interpreted with caution due to the presence of significant heterogeneity and the small number of the randomized, controlled trials included.

Keywords: Wound and injuries; Trauma severity indices; Shock, hemorrhagic; Fluid therapy/methods; Hemodynamics/physiology

INTRODUCTION

Trauma is the most common cause of mortality and morbidity in adults younger than 40 years old, accounting for significant 'life years' lost through premature death and disability. Strategies to improve the outcomes of trauma victims are therefore imperative.[1] Hemorrhagic shock associated with major trauma leads to a decrease in global oxygen delivery and vital organ perfusion. In addition to the initial insult of the trauma, subsequent surgical interventions place increased physiological demands on the patient.

Inability to meet the demand for oxygen delivery results in an anaerobic metabolism, accumulation of metabolic waste products, and eventually organ failure.[2]

The hemodynamic management of hypovolemic shock secondary to trauma can be divided into 3 distinct phases.[3] The first phase includes the period from injury to definitive surgical/radiological management and hemostasis. The second phase describes the immediate postoperative period, and the third phase encompasses the period in the intensive care unit (ICU) that follows definitive surgical care.

The first phase usually occurs during the pre- and early hospital periods. Early initiation of fluid resuscitation and rapid control of hemorrhage limit the duration of the first stage of trauma.[2] The use of a 'hypotensive resuscitation' strategy in penetrating torso injuries has been associated with significant reductions in blood product requirements, fluid administration, postoperative coagulopathy and death.[4,5] However, there are no clear benefits of hypotensive resuscitation strategies in blunt trauma or in the presence of concomitant brain injury.

The second and third phases usually occur during the postoperative period in the ICU. Systemic inflammatory response syndrome (SIRS) associated with the initial trauma and subsequent surgery increases the oxygen demand. Failure to increase global oxygen delivery to match the oxygen deficit resulting from major surgery and trauma has been associated with increased incidences of organ failure and death.[6]

Pioneering observational studies have found that survivors of severe trauma and high-risk surgery were consistently able to achieve higher values of cardiac index and global oxygen delivery, compared with non-survivors.[7,8] Hemodynamic values of survivors have therefore been used as targets of resuscitation in landmark studies by Shoemaker et al.[7] and Fleming et al.,[8] resulting in improved outcomes.

Several further trials have added to a now strong body of evidence suggesting that the use of goal-directed therapy (GDT) is associated with improved outcomes in high-risk surgical patients.[9-13] Protocolized goal-managed care has also been shown to improve outcomes in patients with sepsis[14] and in potential organ donors.[15] Similarities exist between patients undergoing major surgery and those undergoing major trauma, including the SIRS response and associated increased oxygen demand. However, evidence supporting the use of GDT in trauma patients has been limited. We investigated the effects on mortality of GDT following major trauma. Secondary outcomes included complication rates, hospital and ICU length of stay and volumes of fluids and blood administered.

METHODS

We performed this systematic review and meta-analysis following pre-specified criteria, using the PRISMA guidelines.[16]

Eligibility criteria

Only studies involving severe trauma patients were included. Severe trauma was defined as the presence of an injury severity score (ISS) of 15 or greater.[17,18] Randomized, controlled trials (RCT) reporting mortality and complications were included. GDT was defined as the use of hemodynamic monitoring and therapies to achieve pre-determined hemodynamic endpoints during trauma resuscitation and the immediate postoperative phase. Studies were included if they used hemodynamic optimization following a clear protocol, with step-by-step instructions for the clinician to provide interventions based on data obtained by hemodynamic monitors.

Burns, head injuries, pediatric populations and studies including other (non-trauma) critically ill patients were excluded.

Information sources and search strategy

MedLine (via Ovid), Embase (via Ovid) and the Cochrane Controlled Clinical Trials Register (CENTRAL, issue 5 of 2012) were searched for suitable studies. No date restrictions were applied to MedLine or CENTRAL. Embase was restricted to 2009-2013.[19] Search terms were entered into the databases using a Cochrane highly sensitive search strategy[20] (Appendix 1), and these terms included 'goal-directed therapy, hemodynamic, optimization, goal oriented, goal targeted, cardiac output, cardiac index, oxygen delivery, oxygen consumption, cardiac volume, stroke volume, fluid therapy, fluid loading, supranormal, trauma, traumatic and injury'. We defined 'supranormal' physiological targets as a DO_2L of >600mL/min/m² or a cardiac index >4.5L/min/m².

Two of the authors (CC, NA) independently screened titles and abstracts to exclude non-relevant studies. Full-text articles were then appraised against the inclusion criteria. Data were extracted from the selected studies using a pre-designed data collection form, by the same two authors (CC, NA). A third author (MC) resolved discrepancies arising from the data collection.

Methodological quality assessment

The included RCTs were analyzed for methodological quality using the scale designed by Jadad et al.[21] This scale appraises RCTs in terms of the methods used for random assignment and blinding and the flow of patients in the trial. The scale ranges from a score of 0 (lowest quality) to 5 (highest quality). We did not exclude studies based on their Jadad scores.

Outcomes analysis

Hospital mortality was the primary outcome measurement of this study. Secondary outcomes were hospital and ICU length of stay, complication rates, and volumes of fluids and blood administered.

Statistical analysis

Dichotomous outcomes are reported as odds ratios (OR) using a Mantel Haenszel random effects method (with 95% confidence intervals [95%CI]). Differences in continuous outcomes are reported using a random-effects inverse variance model, as the mean difference (MD) and standard mean difference (SMD) when individual studies report outcomes using different scales.[20] P values were two tailed and considered to be statistically significant if <0.05. The chi-square test and between-study variance τ^2 were used to assess heterogeneity with a statistical significance value for heterogeneity set at a p value of <0.1. Inconsistency was assessed using the I^2 methodology and was considered to be high if >40%.[22] The statistical analyses were performed using RevMan software, version 5.1 (Cochrane Rev manager; 2012).

RESULTS

Study populations

The search strategy retrieved 4920 studies. Following screening of titles and abstracts, 305 references were identified as potentially relevant to hemodynamic optimization in trauma. Further review of the abstracts against our inclusion criteria produced 196 titles with potential for further analysis. After reviewing these abstracts, 29 full-text titles were then assigned for further analysis. Twenty-three studies were excluded because they were not RCT. A total of 6 RCT were identified. Of these, one RCT was excluded on the basis of including a mixed population of critically ill patients with and without trauma,[23] and another was excluded because the hemodynamic goals did not differ in the treatment and control groups.[24] Four titles were identified as RCTs suitable for statistical analysis[8,25-27] (Figure 1).
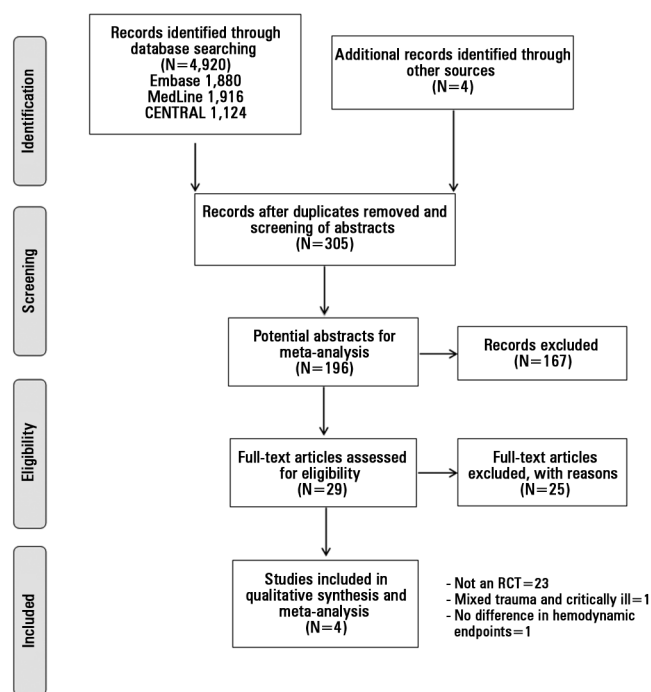

Figure 1 - Flow diagram of search process and study selection as suggested by the preferred reporting items for systematic reviews and meta-analysis (PRISMA). RCT - randomized controlled trials.

The year of publication ranged from 1992 to 2007, and the study sizes varied between 67 and 162 patients. A total of 419 patients were included in the analysis, with 203 in the GDT protocol group and 216 in the control group. The 4 studies analyzed were single-center trials and included patients with severe trauma (ISS>15) and significant blood loss (>2000mL). The median Jadad score of the included studies was 2 (Table 1).

Description of studies

Bishop et al.[25] and Fleming et al.[8] used the pulmonary artery catheter (PAC), whereas Chytra et al.[26] used the oesophageal Doppler monitor (ODM), and Velmahos et al.[27] used thoracic bioimpedance with or without the PAC. In 3 of the 4 studies, supranormal hemodynamic DO_2I and cardiac index were targeted in the GDT group using PAC-guided fluid and inotrope therapy. The other study, utilizing the ODM, used fluids to achieve a specific corrected flow time (FTc>0.35s) and to optimize stroke volume. All of the studies commenced the optimization protocol within 12 hours of admission to the hospital or surgery (Table 2).

Mortality

All 4 of the RCT included reported mortality as a primary outcome. A total of 36 patients (17.7%) in the GDT treatment group and 61 patients (28%) in the control group died. Overall, there was a significant reduction in the relative risk of mortality in the GDT group (OR 0.56; 95%CI: 0.34-0.92; p=0.02, I^2=3%), compared to the control group (Figure 2).

Intensive care and Hospital length of stay

Hospital and ICU length of stay were reported in all 4 of the trials. There was significant heterogeneity between the included trials for these outcomes. Patients receiving hemodynamic optimization had significantly shorter ICU (MD 3.7 days, 95%CI: 1.06-6.5, p=0.006, I^2=98%) (Figure 3) and hospital length of stay (MD 3.5 days, 95%CI: 2.75-4.25, p<0.00001, I^2=44%) (Figure 4) than the patients in the control group.

Table 1 - Randomized clinical trials of goal-directed therapy in severe trauma patients

Author/year	Patients protocol group (N)	Patients control group (N)	Monitor protocol group	Type of intervention	Goals protocol group	Goals control group	Mortality protocol group N (%)	Mortality control group N (%)	Jadad score
Fleming, 1992[8]	33	34	PAC	Fluids + Dobutamine	DO_2I>670mL/min/m² VO_2>166mL/mim/m² CI>4.5L/min/m²	SBP>120mmHg HR<110bpm Hb>10g/dL UO 30-50mL/h CVP 8-12mmHg	8 (24)	15 (44)	1
Bishop, 1995[25]	50	65	PAC	Fluids + Dobutamine	DO_2I>670mL/min/m² VO_2>166mL/mim/m² CI>4.5L/min/m² Hb up to 14g/dL	SBP>120mmHg HR<110bpm Hb>10g/dL UO 30-50mL/h CVP 8-12mmHg	9 (18)	24 (37)	1
Chytra, 2007[26]	80	82	ODM	Fluids	FTC>0.35, SV	CVP 12-15mmHg MAP>65 SpO_2>95,% HR<100bpm UO>1mL/kg/h T 37º C Hb>8.5			
Velmahos, 2000[27]	40	35	Thoracic bioimpedance/ PAC	Fluids ± inotropes ± vasopressors	SBP>100mmHg Hct>30% UO>1mL/lg/h BE<-3 CI>4.5L/min/m² $P_{tc}O_2/FiO_2$>200 If PAC DO_2I>600mL/min/m² VO_2I>170mL/min/m²	SBP>100mmHg Hct>30% UO>1mL/lg/h BE<-3 CI>4.5L/min/m² $P_{tc}O_2/FiO_2$>200 If PAC DO_2I>450mL/min/m² VO_2I>130mL/min/m²	6 (15)	4 (11)	3

PAC - pulmonary artery catheter; DO_2I - oxygen delivery index; VO_2 - oxygen consumption; CI - cardiac index; SBP - systolic blood pressure; HR - heart rate; bpm - beats per minute; Hb - hemoglobin; UO - urinary output; CVP - central venous pressure; ODM - oesophageal Doppler monitor; FTC - flow time corrected; MAP - mean arterial pressure; SpO_2 - oxygen saturation; T - temperature; Hct - hematocrit; BE - base excess; $P_{tc}O_2/FiO_2$ - ratio of transcutaneous oxygen tension to fractional inspired oxygen.

Table 2 - Fluid and blood administration volumes

Author/year	Timing intervention	Period of volume infusion reported	Total fluids protocol group (mL) (mean±SD)	Total fluids control group (mL) (mean±SD)	RBC transfused protocol group (mean±SD)	RBC transfused control group (mean±SD)
Fleming, 1992[8]	Within 6 hours after surgery/admission	Admission to 48 hours post-operatively	Crystalloid: 13,247±1,377 Colloid: 4097±552	Crystalloid: 16,943±1,558 Colloid: 2,528±781	5,848±920mL	6,423±1,234mL p<0.01
Bishop, 1995[25]	Within 6 hours after surgery or 12 hours after admission	Admission to 48 hours post-operatively	Crystalloid: 9,065±772 Colloid: 3,038±391	Crystalloid: 9,197±649 Colloid: 1,352±330 p<0.00001	4,304±575mL	2,715±513mL p<0.0001
Chytra, 2007[26]	ICU admission	12 hours post-operatively	Crystalloid: 1,667±426 Colloid: 1,293±300	Crystalloid: 1,334±320 p=0.38 Colloid: 682±322 p<0.0001	814±228mL	833±340mL
Velmahos, 2000[27]	On arrival to hospital	24 hours from admission	14,000±6,500	13,000±6,000	11±10.5 units	11±7 units

MI - milliliters; ICU - intensive care unit.
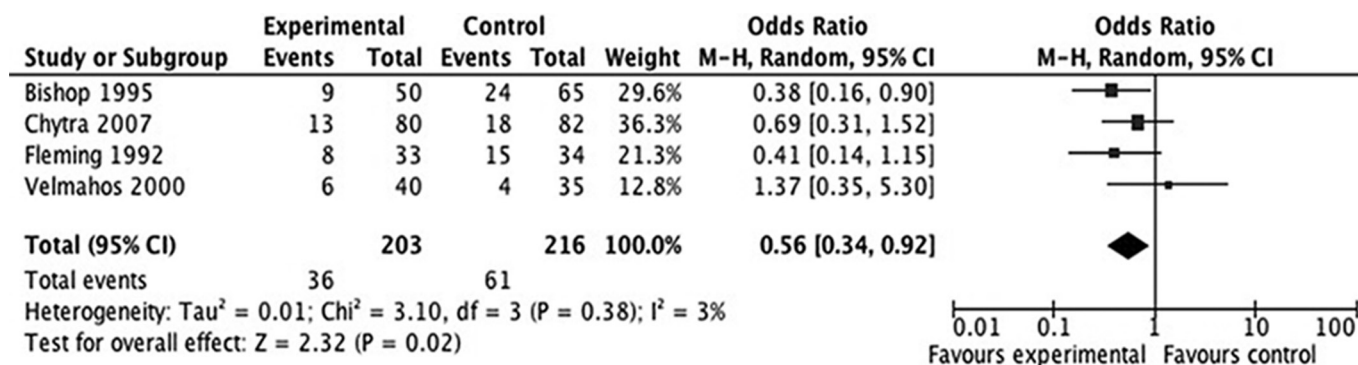
Figure 2 - Effects of goal-directed therapy in protocol group versus control group on mortality.
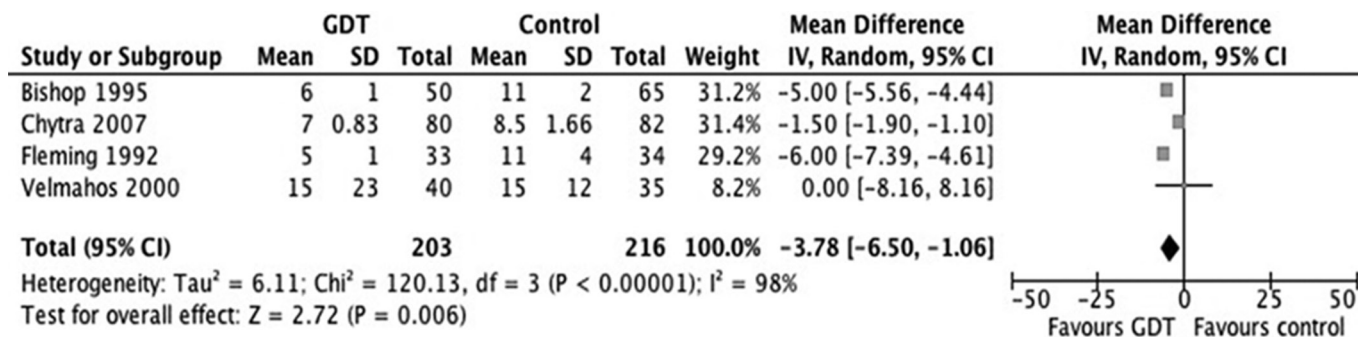
Figure 3 - Effects of goal-directed therapy in protocol group versus control group on intensive care unit length of stay.

Complications and organ failure

Quantitative analysis of complications was not possible due to variations in the reporting of data among the studies. Three of the 4 studies demonstrated reductions in complication rates associated with early GDT.[8,25,26] Fleming showed a reduction in the number of organ failure events per patient in the protocol group, compared with the control group (0.79±0.68 versus 1.74±1.64; p=0.05).[10] Similar results were demonstrated by Bishop et al. (0.74±0.28 versus 1.68±0.28, p<0.05 for the protocol group compared

Study or Subgroup	GDT Mean	GDT SD	GDT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Bishop 1995	12	1	50	16	2	65	47.1%	-4.00 [-4.56, -3.44]
Chytra 2007	14	2.08	80	17.5	3	82	37.3%	-3.50 [-4.29, -2.71]
Fleming 1992	13	3	33	15	4	34	15.1%	-2.00 [-3.69, -0.31]
Velmahos 2000	25	24	40	27	21	35	0.5%	-2.00 [-12.18, 8.18]
Total (95% CI)			203			216	100.0%	-3.50 [-4.25, -2.75]

Heterogeneity: Tau² = 0.23; Chi² = 5.34, df = 3 (P = 0.15); I² = 44%
Test for overall effect: Z = 9.13 (P < 0.00001)

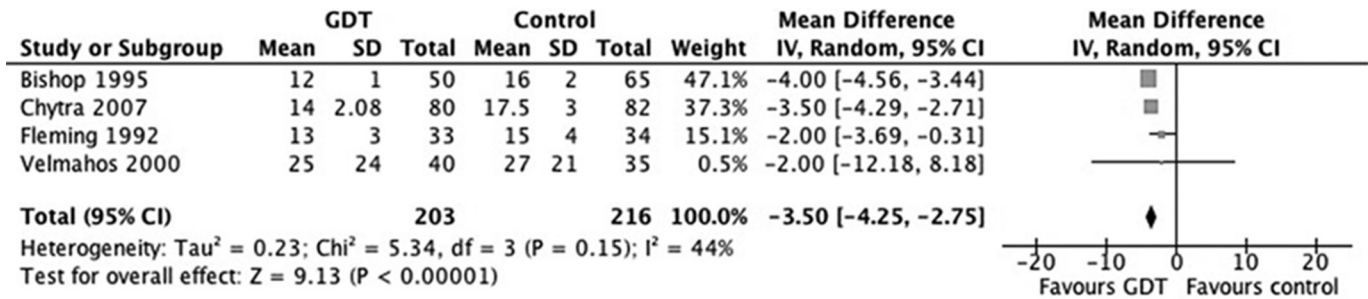**Figure 4 -** Effects of goal directed therapy in protocol group versus control group on hospital length of stay.

to the control group, respectively).[25] In the study by Chytra, the relative risk of infectious complications was lower among patients in the GDT group, compared to the control group (RR 0.5491, 95%CI: 0.31-0.95; p=0.032).[26] In contrast to the other studies, Velmahos et al. found no differences in complication rates between the treatment and control groups.[27]

Red cell transfusion and fluid administration requirements

Quantitative analysis showed significant heterogeneity between the trials and did not demonstrate a significant difference in blood transfusion requirements between the GDT and control groups. (SMD=0.58, 95%CI: -0.74-1.89, p=0.39, I²=97%) (Figure 5). Only the study by Bishop et al. reported a statistically significantly greater red blood cell transfusion requirement in the GDT group (4,304±575mL), compared to the control group (2,715±513mL, p<0.0001)[25] (Table 2). Similarly, there were no significant differences in the total volume of fluid administered during the studies (SMD=0.65, 95%CI: -0.84-2.15 p=0.39, I²=98%) (Figure 6). Bishop et al. reported however, a significantly greater volume of colloid administered in the GDT group, compared to the control group (3,038±391mL versus 1,352±330, respectively, p<0.00001). Similarly, Chytra et al.[26] reported a significantly greater mean volume of colloid administered to the treatment group, compared to the control group (1,667±426mL versus 682±322mL, p<0.0001, respectively) (Table 2).

DISCUSSION

In this meta-analysis, GDT was associated with a beneficial effect on mortality in patients with major trauma. Three of the 4 studies used the PAC, because most of the studies were conducted prior to widespread use of minimally invasive cardiac output monitors. The potential benefits of the newer hemodynamic monitors used to assess the adequacy of resuscitation in trauma patients[28,29] warrant further RCTs.

The evidence supporting perioperative GDT for the high-risk surgical patient has shown that, when hemodynamic optimization is initiated early and delivered using a clearly defined protocol,[9,30] morbidity (and for high-risk groups also mortality) is decreased postoperatively. This review was performed to ascertain whether GDT during the second and third phases of major trauma conferred any benefit.

Fluid resuscitation that forms part of GDT, might increase the risks of intra-abdominal hypertension and abdominal compartment syndrome among trauma patients undergoing GDT.[31] However, we found no significant difference in the total volume of fluid administered, although firm conclusions were not possible due to differences in study duration. In addition, none of the studies included in this review included data on the incidence of intra-abdominal hypertension.

There might be concerns that an increase in global oxygen delivery could increase perfusion pressure, resulting in more bleeding complications and greater transfusion requirements. Although we found no differences in transfusion requirements between the GDT and control groups of patients, none of the studies reported the final hemoglobin concentrations between treatment and control groups, and there were significant differences in the transfusion protocols among the studies. Differences in transfusion requirements in the treatment and control groups should therefore be interpreted with caution. Furthermore, GDT should be considered only after adequate hemostasis has been achieved.
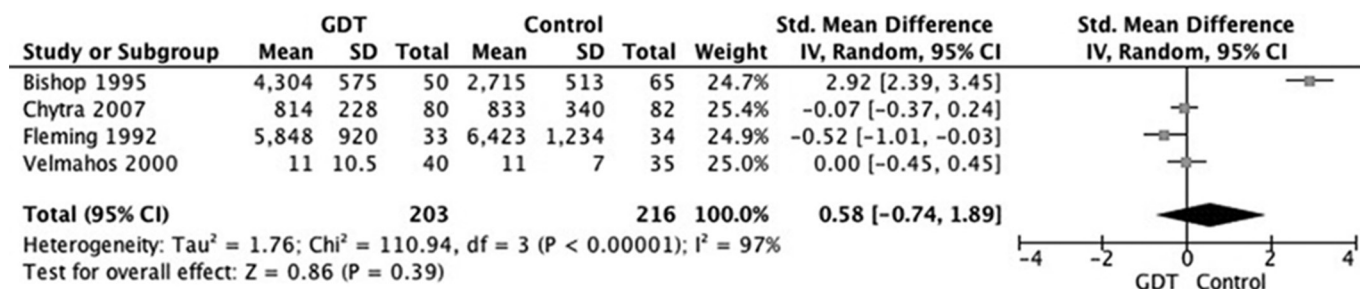
Study or Subgroup	GDT Mean	GDT SD	GDT Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bishop 1995	4,304	575	50	2,715	513	65	24.7%	2.92 [2.39, 3.45]
Chytra 2007	814	228	80	833	340	82	25.4%	-0.07 [-0.37, 0.24]
Fleming 1992	5,848	920	33	6,423	1,234	34	24.9%	-0.52 [-1.01, -0.03]
Velmahos 2000	11	10.5	40	11	7	35	25.0%	0.00 [-0.45, 0.45]
Total (95% CI)			**203**			**216**	**100.0%**	**0.58 [-0.74, 1.89]**

Heterogeneity: Tau^2 = 1.76; Chi^2 = 110.94, df = 3 (P < 0.00001); I^2 = 97%
Test for overall effect: Z = 0.86 (P = 0.39)

Figure 5 - Effects of goal directed therapy in protocol group versus control group on blood transfusion requirements.

Study or Subgroup	GDT Mean	GDT SD	GDT Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bishop 1995	12,103	865	50	10,549	728	65	25.0%	1.95 [1.50, 2.40]
Chytra 2007	2,960	521	80	2,016	453	82	25.2%	1.93 [1.55, 2.30]
Fleming 1992	17,344	1,483	33	19,471	1,396	34	24.8%	-1.46 [-2.00, -0.92]
Velmahos 2000	14,000	6,500	40	13,000	6,000	35	25.0%	0.16 [-0.30, 0.61]
Total (95% CI)			**203**			**216**	**100.0%**	**0.65 [-0.84, 2.15]**

Heterogeneity: Tau^2 = 2.27; Chi^2 = 132.81, df = 3 (P < 0.00001); I^2 = 98%
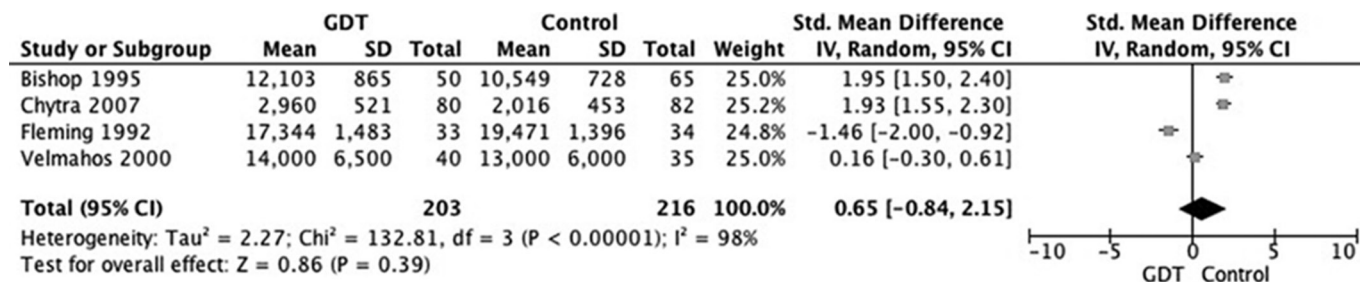Test for overall effect: Z = 0.86 (P = 0.39)

Figure 6 - Effects of goal directed therapy in protocol group versus control group on total volume of fluids administered.

The main limitations of this meta-analysis were the small number of studies and the lack of recent studies, with the publication dates spanning more than 20 years. Significant heterogeneity among the included studies was present and was accounted for by applying the more conservative random effects model in the meta-analysis. Although it was not possible to perform a quantitative analysis of morbidity or organ failure, most of the studies reviewed suggested a trend toward a beneficial effect of GDT in trauma. Furthermore, we acknowledge that the definitions and coding of complications were likely to vary among the studies. We analyzed the data extracted from studies, rather than the data of individual patients. Not all of the studies included were of a high-quality design, as reflected by the median Jadad score of 2.

Because surgical techniques, peri-operative care, and patient selection have been refined over the years, the overall mortality of high-risk surgical patients has improved. This change was recently evaluated in a meta-analysis of 29 peri-operative GDT trials performed between 1995 and 2008.[9] There was an approximate halving of mortality rates in the control group every decade (29.5%, 13.5%, 7%). As such, the applicability of historical trials to current-day practice might not be valid. Due to the small number of studies, it was not possible to ascertain the effects of time on the mortality rates of trauma patients, and up-to-date RCTs are required.

CONCLUSION

Hemodynamic optimization using a pre-defined protocol and started early in the course of the perioperative period of patients with severe traumatic injury was associated with a mortality benefit and might also reduce the incidence of organ failure. The current results should be interpreted with caution due to the significant statistical heterogeneity present and the small number of randomized controlled trials included. Further randomized controlled trials, set within current trauma and hemodynamic optimization practices, are desirable.

Author's contributions

C Corredor and N Arulkumaran: study design, literature search, statistics and writing of the manuscript; M Cecconi: study design and manuscript editing; J Ball, MA Hamilton, MR Grounds and A Rhodes: manuscript editing.

RESUMO

Objetivo: O trauma grave pode associar-se a ocorrência de importante choque hemorrágico e ao comprometimento da perfusão dos órgãos. Formulamos a hipótese de que o tratamento direcionado por objetivo conferiria benefícios em termos de morbidade e mortalidade, em casos graves de trauma.

Métodos: Realizamos uma busca sistemática nas bases de dados MedLine, Embase e *Cochrane Controlled Clinical Trials Register* com relação a pacientes vítimas de trauma grave. A mortalidade foi o desfecho primário dessa revisão. Os desfechos secundários incluíram taxas de complicações, duração da permanência no hospital e na unidade de terapia intensiva, e o volume de fluidos administrados. A metanálise foi realizada utilizando o programa de computador RevMan, e os dados apresentados são as *odds ratios* (OR) para desfechos dicotomizados e as diferenças médias e diferenças médias padrão para desfechos contínuos.

Resultados: Foram analisados quatro estudos clínicos randomizados e controlados, que incluíram 419 pacientes. O risco de mortalidade foi significantemente reduzido nos pacientes com tratamento direcionado por objetivo, em comparação ao grupo controle (OR=0,56; IC95%: 0,34-0,92). A duração da permanência na unidade de terapia intensiva (DM: 3,7 dias; IC95%: 1,06-6,5) e no hospital (DM: 3,5 dias; IC95%: 2,75-4,25) foi significativamente mais curta no grupo de pacientes do grupo tratado conforme o protocolo. Não houve diferenças nos relatos relativos a volume total de fluidos infundidos e a transfusões sanguíneas. A heterogeneidade nos relatos entre os estudos impediu uma análise quantitativa das complicações.

Conclusão: Após a ocorrência de trauma grave, o uso precoce de tratamento direcionado por objetivo se associou com mortalidade mais baixa e com menos dias de permanência na unidade de terapia intensiva e no hospital. Os achados desta análise devem ser interpretados com cautela, em razão da importante heterogeneidade e do número pequeno de estudos clínicos randomizados e controlados, que foram incluídos na análise.

Descritores: Ferimentos e lesões; Índices de gravidade do trauma; Choque hemorrágico; Hidratação/métodos; Hemodinâmica/fisiologia

REFERENCES

1. Christensen MC, Ridley S, Lecky FE, Munro V, Morris S. Outcomes and costs of blunt trauma in England and Wales. Crit Care. 2008;12(1):R23.

2. Brochner AC, Toft P. Pathophysiology of the systemic inflammatory response after major accidental trauma. Scand J Trauma Resusc Emerg Med. 2009;17:43.

3. Lucas CE. Update on trauma care in Canada. 4. Resuscitation through the three phases of hemorrhagic shock after trauma. Can J Surg. 1990;33(6):451-6.

4. Bickell WH, Wall MJ Jr, Pepe PE, Martin RR, Ginger VF, Allen MK, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med. 1994;331(17):1105-9.

5. Morrison CA, Carrick MM, Norman MA, Scott BG, Welsh FJ, Tsai P, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. J Trauma. 2011;70(3):652-63.

6. Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. Arch Surg. 1973;106(5):630-6.

7. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest. 1988;94(6):1176-86.

8. Fleming A, Bishop M, Shoemaker W, Appel P, Sufficool W, Kuvhenguwha A, et al. Prospective trial of supranormal values as goals of resuscitation in severe trauma. Arch Surg. 1992;127(10):1175-9; discussion 1179-81.

9. Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. Anesth Analg. 2011;112(6):1392-402.

10. Poeze M, Greve JW, Ramsay G. Meta-analysis of hemodynamic optimization: relationship to methodological quality. Crit Care. 2005;9(6):R771-9.

11. Dalfino L, Giglio MT, Puntillo F, Marucci M, Brienza N. Haemodynamic goal-directed therapy and postoperative infections: earlier is better. A systematic review and meta-analysis. Crit Care. 2011;15(3):R154.

12. Giglio MT, Marucci M, Testini M, Brienza N. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. Br J Anaesth. 2009;103(5):637-46.

13. Arulkumaran N, Corredor C, Hamilton MA, Ball J, Grounds RM, Rhodes A, et al. Cardiac complications associated with goal-directed therapy in high-risk surgical patients: a meta-analysis. Br J Anaesth. 2014;112(4):648-59.

14. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, Schorr C, Artigas A, Ramsay G, Beale R, Parker MM, Gerlach H, Reinhart K, Silva E, Harvey M, Regan S, Angus DC; Surviving Sepsis Campaign. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Crit Care Med. 2010;38(2):367-74.

15. Westphal GA, Zaclikevis VR, Vieira KD, Cordeiro Rde B, Horner MB, Oliveira TP, et al. A managed protocol for treatment of deceased potential donors reduces the incidence of cardiac arrest before organ explant. Rev Bras Ter Intensiva. 2012;24(4):334-40.

16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.

17. Baker SP, O'Neill B, Haddon W Jr, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma. 1974;14(3):187-96.

18. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. Trauma Score and the Injury Severity Score. J Trauma. 1987;27(4):370-8.

19. Lefebre C, Manheimer E, Glanville J. Searching for studies. In: Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of interventions. Version 5.0.1. (updated September 2008). 2008. [cited 2012 April 11]. Available from http://hiv.cochrane.org/sites/hiv.cochrane.org/files/uploads/Ch06_Searching.pdf

20. Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011 [cited 2012 April 11]. Available from http://www.cochrane-handbook.org

21. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.

22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. Review.

23. Durham RM, Neunaber K, Mazuski JE, Shapiro MJ, Baue AE. The use of oxygen consumption and delivery as endpoints for resuscitation in critically ill patients. J Trauma. 1996;41(1):32-9; discussion 39-40.

24. Ivatury RR, Simon RJ, Islam S, Fueg A, Rohman M, Stahl WM. A prospective randomized study of end points of resuscitation after major trauma: global oxygen transport indices versus organ-specific gastric mucosal pH. J Am Coll Surg. 1996;183(2):145-54.

25. Bishop MH, Shoemaker WC, Appel PL, Meade P, Ordog GJ, Wasserberger J, et al. Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma. J Trauma. 1995;38(5):780-7.

26. Chytra I, Pradl R, Bosman R, Pelnár P, Kasal E, Zidková A. Esophageal Doppler-guided fluid management decreases blood lactate levels in multiple-trauma patients: a randomized controlled trial. Crit Care. 2007;11(1):R24.

27. Velmahos GC, Demetriades D, Shoemaker WC, Chan LS, Tatevossian R, Wo CC, et al. Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial. Ann Surg. 2000;232(3):409-18.

28. Burns JM, Sing RF, Mostafa G, Huynh TT, Jacobs DG, Miles WS, et al. The role of transesophageal echocardiography in optimizing resuscitation in acutely injured patients. J Trauma. 2005;59(1):36-40; discussion 40-2.

29. Kohli-Seth R, Neuman T, Sinha R, Bassily-Marcus A. Use of echocardiography and modalities of patient monitoring of trauma patients. Curr Opin Anaesthesiol. 2010;23(2):239-45. Review.

30. Cecconi M, Corredor C, Arulkumaran N, Abuella G, Ball J, Grounds RM, et al. Clinical review: Goal-directed therapy-what is the evidence in surgical patients? The effect on different risk groups. Crit Care. 2013;17(2):209.

31. Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Valdivia A, Sailors RM, et al. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. Arch Surg. 2003;138(6):637-42; discussion 642-3.

Appendix 1 - Search strategies

1. MedLine database (OVID interface): the Cochrane highly sensitive search strategy was used:
#1. randomized Controlled Trials as Topic/
#2. randomized controlled trial/
#3. random Allocation/
#4. double Blind Method/
#5. single Blind Method/
#6. clinical trial/
#7. controlled clinical trial.pt.
#8. randomized controlled trial.pt.
#9. multicenter study.pt.
#10. clinical trial.pt.
#11. exp Clinical Trials as topic/
#12. or/1-11
#13. (clinical adj trial$).tw.
#14. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
#15. randomly allocated.tw.
#16. (allocated adj2 random$).tw.
#17. or/13-16
#18. 12 or 17
#19. case report.tw.
#20. letter/
#21. historical article/
#22. or/19-21
#23. 18 not 22
#24. exp trauma/
#25. trauma.tw.
#26. trauma.mp.

... continuation

#27. 24 or 25 or 26
#28. exp trauma$/
#29. Trauma$.tw.
#30. Trauma$.mp
#31. 28 or 29 or 30
#32. Exp injury/
#33. Injury.tw.
#34. Injury.mp.
#35. 32 or 33 or 34
#36. 27 or 31 or 35
#37. exp goal directed/ or goal directed.tw. or goal directed.mp.
#38. exp goal oriented/ or goal oriented.tw. or goal oriented.mp.
#39. exp goal target/ or goal target.tw. or goal target.mp.
#40. exp cardiac output/ or cardiac output.tw. or cardiac output.mp.
#41. exp cardiac index/ or cardiac index.tw. or cardiac index.mp.
#42. exp oxygen delivery/ or oxygen delivery.tw. or oxygen delivery.mp.
#43. exp oxygen consumption/ or oxygen consumption.tw. or oxygen consumption.mp
#44. exp cardiac volume/ or cardiac volume.tw. or cardiac volume.mp.
#45. exp stroke volume/ or stroke volume.tw. or stroke volume.mp.
#46. exp fluid therapy/ or fluid therapy.tw. or fluid therapy.mp.
#47. exp fluid loading/ or fluid loading.tw. or fluid loading.mp.
#48. exp fluid administration/ or fluid administration.tw. or fluid administration.mp.
#49. exp optimization/ or optimization.tw. or optimization.mp.
#50. exp optimization/ or optimisation.tw. or optimisation.mp.
#51. exp supranormal/ or supranormal.tw. or supranormal.mp.
#52. exp lactate/ or lactate.tw. or lactate.mp.
#53. exp extraction ratio/ or extraction ratio.tw. or extraction ratio.mp.

#54.	37 or 38 or 39 or 40 or 41or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
#55.	23 and 36 and #54

2. Embase (OVID interface):

#1.	Clinical Trial/
#2.	Randomized controlled trial/
#3.	Randomization/
#4.	Single blind procedure/
#5.	Double blind procedure/
#6.	Crossover procedure/
#7.	Placebo/
#8.	Randomi?ed controlled trial$.tw.
#9.	Rct.tw.
#10.	Random allocation.tw.
#11.	Random allocated.tw
#12.	Allocated randomly.tw.
#13.	(allocated adj2 random).tw.
#14.	Single blind$.tw.
#15.	Double blind$.tw.
#16.	Placebo$.tw
#17.	Prospective study/
#18.	Or/1-17
#19.	Case study/
#20.	Case report.tw.
#21.	Abstract report/or letter/
#22.	Or/19-21
#23.	18 not 22
#24.	trauma
#25.	exp trauma/or trauma
#26.	traum$
#27.	24 or 25 or 26
#28.	Injury
#29.	exp injury/or injury
#30.	27 or 28
#31.	26 or 29
#32.	exp heart/ or heart.mp.) and output.mp.
#33.	exp heart output/ or heart output.mp.
#34.	goal directed
#35.	goal oriented
#36.	goal target
#37.	exp heart index/ or heart index.mp.
#38.	exp heart stroke volume/ or heart stroke volume.mp.

Continue...

#39.	exp oxygen consumption/ or oxygen consumption.mp.
#40.	oxygen delivery.mp.
#41.	exp fluid therapy/
#42.	fluid administration.mp.
#43.	fluid loading.mp.
#44.	hemodynamic.mp
#45.	supranormal.mp.
#46.	optimisation.mp.
#47.	optimization.mp.
#48.	exp lactate/
#49.	extraction ratio.mp
#50.	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
#51.	23 and 30 and 49

3. Cochrane clinical trials database (CENTRAL):

#1.	trauma in Trials
#2.	Trauma* in Trials
#3.	traumatic* in Trials
#4.	Injury* in Trials
#5.	1 OR 2 OR #3 OR 4
#6.	cardiac near output* in trials
#7.	cardiac near volume* in Trials
#8.	cardiac near index* in Trials
#9.	oxygen near delivery* in Trials
#10.	oxygen near consumption* in Trials
#11.	supranormal* in Trials
#12.	stroke near volume* in Trials
#13.	fluid near therapy* in Trials
#14.	fluid near administration* in Trials
#15.	fluid near loading* in Trials
#16.	extraction near ratio* in Trials
#17.	lactate* in Trials
#18.	goal near directed* in Trials*
#19.	goal near oriented* in Trials
#20.	goal near target* in Trials
#21.	Hemodynamic near optimization* in trials
#22.	Hemodynamic near optimization * in trials
#23.	Optimization* in trials
#24.	Optimisation* in trials
#25.	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
#26.	#5 AND#25