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1 **Abstract:**

2 Intracranial pressure (ICP) monitoring is one of the mainstays in the treatment of severe
3 traumatic brain injury (TBI), but different approaches to monitoring exist. The aim of this
4 systematic review and meta-analysis is to compare the effectiveness and complication rate of
5 ventricular drainage (VD) versus intracranial parenchymal (IP) catheters to monitor and treat
6 raised ICP in patients with TBI.

7 Pubmed, EMBASE, Web of Science, Google Scholar and the Cochrane Database were
8 searched for articles comparing ICP monitoring-based management with VDs and monitoring
9 with IP monitors until March 2018. Study selection, data extraction and quality assessment
10 were performed independently by two authors. Outcomes assessed were mortality, functional
11 outcome, need for decompressive craniectomy, length of stay, overall complications, such as
12 infections, and hemorrhage. Pooled effect estimates were calculated with random effects
13 models and expressed as relative risk (RR) for dichotomous outcomes and mean difference
14 (MD) for ordinal outcomes, with corresponding 95% confidence intervals (CI).

15 Six studies were included: 1 randomized controlled trial and 5 observational cohort studies.
16 Three studies reported mortality, functional outcome and the need for a surgical
17 decompression, three only reported complications. Quality of the studies was rated as poor,
18 with critical or serious risk of bias. The pooled analysis did not show a statistically significant
19 difference in mortality (RR=0.90, 95% CI=0.60 to 1.36, p=0.41) or functional outcome
20 (MD=0.23, 95% CI=0.67 to 1.13, p=0.61). The complication rate of VDs was higher
21 (RR=2.56, 95% CI=1.17 to 5.61, p= 0.02) and consisted mainly of infectious complications,
22 i.e. meningitis.

23 VDs caused more complications, particularly more infections but there was no difference in
24 terms of mortality or functional outcome between the two monitoring modalities. However,
25 the studies had a high risk of bias. A need exists for high quality comparisons of VDs versus
26 IP monitor-based management strategies on patient outcomes.

27 **Keywords:** ICP monitoring; Ventricular Catheters; Intraparenchymal monitors; Monitoring
28 Devices; Patient Outcomes; Severe TBI

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2 **Introduction**

3 Intracranial pressure (ICP) monitoring is one of the mainstays of current severe traumatic
4 brain injury (TBI) treatment at the ICU and guidelines recommend using ICP monitoring in
5 order to reduce mortality.¹

6 There is a wide range of intracranial pressure sensors. Two types are most commonly used:
7 Ventricular drainage (VD) and intraparenchymal catheters. The IP monitor catheters require a
8 small opening in the skull and their small diameters cause little damage to the brain
9 parenchyma. They have a low risk of infection and other complications, such as intracerebral
10 hemorrhage.² The insertion of a ventricular catheter, usually into the frontal horn of the right
11 lateral ventricle, requires a relatively larger opening and is thought to cause more damage to
12 brain tissue than the insertion of a smaller parenchymal sensor.³ VDs fulfill two objectives:
13 besides monitoring, they permit drainage of CSF, thereby acting as an ICP-lowering
14 intervention. However, this is accomplished at the expense of an increased risk of infections
15 and complications.²

16 Not much is known about the superiority of one method over the other in terms of patient
17 outcomes. In the second Brain Trauma Foundation Guidelines edition of 2000, in which this
18 topic was addressed, no clear recommendation was made and in subsequent editions the topic
19 was no longer addressed due to lack of evidence.⁴ However, recently, a randomized controlled
20 trial (RCT) was conducted, the first of its kind, that suggested the superiority of VDs over IP
21 monitors on patient outcomes. Next to this single RCT, several observational studies have
22 been published.

23 The aim of this study was to review the available evidence on the effectiveness and
24 complication rate of VD versus IP-monitor-guided treatment of raised ICP in patients with
25 TBI.

26

27 **Materials and methods**

28 A protocol has been published on Prospero.⁵

29 **Search strategy**

30 Searches were not restricted by date, language or publication status. In collaboration with an
31 information specialist from the Erasmus MC library we developed a search strategy
32 (Appendix 1). We performed the search in MEDLINE, EMBASE, ISI Web of Science,
33 Pubmed and Google Scholar, from the first publicly accessible date of a particular database
34 until March 1st, 2018. Ongoing studies were searched on clinicaltrials.gov. Grey literature
35 was screened using Google Scholar and ISI Web of Science. Reference lists of all relevant
36 trials were hand searched and experts in the field that had previously published on this matter
37 were contacted for unpublished literature on this topic.

1 **Ethical approval and consent**

2 This study did not require ethical approval.

3 **Inclusion criteria and study selection**

4 Given the expected scarcity of available literature on the topic, we included – next to RCTs -
5 prospective and retrospective observational studies that described a direct comparison
6 between patients with VDs and patients with IP monitoring and that reported either mortality,
7 functional outcomes or complications. Inclusion criteria were: (1) mainly adult population, (2)
8 severe or moderate TBI on admission defined as a Glasgow coma score (GCS) ≤ 12 and (3)
9 closed head injury

10 Exclusion criteria were (1) penetrating or blast TBI, (2) studies with a predominantly
11 paediatric population, (3) studies without VD and IP comparisons and (4) studies on external
12 lumbar drainage

13 For studies with mixed populations, including mixed ages (i.e. adults and children) and mixed
14 injury types (i.e. TBI and stroke) we included studies in which the results for our population
15 of interest were presented separately, or in which at least 85% of the participants represented
16 our population of interest.

17 Considering mixed injury types, one exception was made in the case of the secondary
18 outcomes, i.e. infections, haemorrhage and catheter malfunctions. Since we did not expect any
19 differences between mixed injury types (i.e. ischaemic stroke and severe TBI) in terms of
20 complications when either device was used. We therefore chose to pool all studies that
21 compared complications in patients with an VD and those with an IP monitor in mixed injury
22 types, even if the population represented $< 85\%$ severe TBI.

23 The first phase involved screening the titles and abstracts (Appendix 3). Studies unrelated to
24 the topics of VDs versus IP monitoring or TBI were excluded. In the second phase the
25 remaining abstracts were screened for the inclusion and exclusion criteria.

26 In the final sifting phase, the full text of the remaining studies was reviewed. Conflicts were
27 resolved by discussion until a final decision was reached.

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29 **Data extraction and risk of bias assessment**

30 Each study was assessed by two investigators (VV, IH) and the data was extracted in a matrix
31 consisting of trial details, such as: trial name and date, trial design, author contact
32 information, inclusion and exclusion criteria, adherence to a published protocol, number of
33 patients, duration of intervention, mean age of patients, mean GCS, percentage of severe TBI,
34 male to female ratio, whether the groups were comparable or not and the effect size and
35 confidence intervals for the primary and secondary outcomes individually (Appendix 2).
36 Finally, potential sources of bias and sources of funding were noted.

1 Quality assessment was performed by two authors independently (VV and JH). For the RCTs
2 we used the Cochrane Collaboration's Risk of Bias Assessment Tool⁶ (assessing the risk of
3 bias as high/low or unknown for each domain) tool and for observational trials the ROBINS-I
4 Cochrane tool⁷ (assessing the studies as low/moderate/serious or critical risk of bias for each
5 domain and overall) (Appendix 4).

6

7 **Outcomes**

8 The primary outcomes were mortality and functional outcome at 6 months or final follow-up
9 if earlier, defined by the Glasgow Outcome Scale/Extended (GOS/E).

10 The secondary outcomes examined were: the need for decompressive craniectomy during ICU
11 stay; the hospital and Intensive Care Unit (ICU) Lengths Of Stay (LOS); **monitoring duration**;
12 device failure at any time point; all complications; infections, however defined in the paper;
13 intracranial haemorrhage; and the number of episodes of refractory intracranial hypertension
14 (RICH), defined as uncontrollable intracranial hypertension by conventional means requiring
15 an increase in therapy intensity, either medical or surgical.

16 We anticipated that all outcome data will be dichotomous. As such, for each study, we have
17 extracted the number of participants receiving each device and the number of events (i.e. n/N)
18 or the GOS mean differences.

19 For the hospital and ICU LOS we calculated the mean difference between groups and the 95%
20 CI.

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23 **Statistical analyses**

24 The relative risk (RR) and corresponding 95% Confidence Interval (CI) were extracted for
25 mortality, need for decompressive craniectomy, overall complications (specifically for device
26 failure, infection and haemorrhage), when available and otherwise calculated.

27 The pooled RR and corresponding 95% CI was then determined using the Mantel-Haenszel
28 approach, and its significance as the true effect estimate was assessed against the null
29 hypothesis RR overall=1 using the z test. Statistical evidence for heterogeneity between
30 studies was assessed using the Q-test and the I² index estimated the between-study variability.
31 We used the random effects model for all analyses, as considerable heterogeneity may exist
32 despite the absence of statistical evidence of this, especially in studies with small sample
33 sizes.

34 **For the outcomes reported as mean difference (MD) ± standard deviation (SD), we used the**
35 **inverse variance method to obtain the pooled MD. In this case we also used the Q-test and I²**
36 **index to estimate statistical heterogeneity between studies. The outcomes were ICU and**
37 **hospital LOS, mean monitoring duration and mean GOS for each group.**

1 Review Manager (RevMan, Cochrane Collaboration, version 5.3) was used for data synthesis.

2

3 **Results**

4 Study characteristics

5 1208 studies underwent abstract screening. Among these, 37 were screened full text
6 (Appendix 3). Six studies were included and characteristics of patients extracted (Appendix 2)
7 with 3968 enrolled patients in total (minimum 122 patients⁸, maximum 2562 patients⁹). One
8 of these was an RCT, the rest were retrospective observational cohorts. Three studies included
9 data on mortality, functional outcome, LOS and surgical decompression, the other three
10 reported only complications.

11 Primary outcome

12 Three studies with 3013 patients reported mortality rates.⁸⁻¹⁰ When the results were
13 aggregated, mortality was not different between VD and IP monitors (RR=0.90, 95% CI=0.60
14 to 1.36, p=0.63). There was substantial heterogeneity ($I^2=76\%$, p value of the Q test=0.01)
15 (*Figure 1a*).

16 In the analysis of studies reporting functional outcome at the end of follow-up, 2 papers
17 involving 451 patients described functional outcome data using the mean GOS difference.^{8,10}
18 When the results were aggregated, mean GOS was not different between the two interventions
19 (Mean Difference (MD) =0.23, 95% CI=-0.67 to 1.13, p=0.61). Heterogeneity was high (Q
20 test p=0.003, $I^2=89\%$) (*Figure 1b*).

21 We contacted the authors of the Kasotakis et al study¹⁰ in order to obtain the absolute
22 numbers of the functional outcome, but the data on these outcomes were not available
23 anymore.

24 Aiolfi et al⁹ only described the absolute numbers for patients functionally independent at
25 discharge. For the 2562 patients described, there was no difference regarding this number
26 between the two groups patients at discharge (RR= 0.97, 95% CI= 0.83 to 1.13).

27 Secondary outcomes

28 Three studies including 3968 patients examined the risk of needing a surgical decompression
29 in both groups.⁸⁻¹⁰ There was no difference between the groups (RR= 0.79, 95% CI= 0.56 to
30 1.10, p=0.16). Heterogeneity was large (Q-test p=0.005; $I^2=81\%$) (*Figure 2a*).

31 The mean LOS in the hospital⁸⁻¹⁰ did not differ between groups with no heterogeneity (MD=
32 0.02, 95% CI= -0.42 to 0.46, p=0.93; Q-test p=0.80; $I^2=0\%$). The mean ICU length of stay
33 was shorter in the IP group (MD= 1.09, 95% CI= 0.41 to 1.78, p=0.002).⁸⁻¹⁰ Heterogeneity
34 was low (Q-test: p=0.25, $I^2=28\%$) (*Figure 2b and 2c*).

1 Two papers including 499 patients reported the mean monitoring duration for both groups.^{8, 10}
2 This did not differ when the results were pooled (MD= 1.78, 95% CI= -1.55 to 5.11, p=0.29).
3 there was large statistical heterogeneity (Q-test: $p < 0.00001$, $I^2=96\%$) (Figure 3e).

4 Three studies including 607 patients reported device failures^{8, 10, 11} and there was no
5 difference between the two groups in this respect (RR=0.98, 95% CI= 0.35 to 2.69, p=0.96).
6 There was a low level of statistical heterogeneity (Q-test $p=0.13$, $I^2= 52\%$) (Figure 3d).

7 Six reports including 3968 patients reported overall complications.^{2, 8-12} Five reports including
8 1406 patients reported infections of the device, hemorrhage and 'all complications'.^{2, 8, 10-12}
9 With regard to all complications, the VD group fared worse than the IP monitor group
10 (RR=2.56, 95% CI=1.17 to 5.61, p= 0.02). Statistical heterogeneity was high (Q-test $p <$
11 0.00001 , $I^2=91\%$) (Figure 3a). Regarding infections^{2, 8, 10-12} in particular, such as meningitis
12 and ventriculitis, VD patients were more at risk (RR=7.09, 95% CI= 2.64 to 19.04, p=0.0001),
13 without evidence of statistical heterogeneity (Q-test $p=0.59$, $I^2= 0\%$) (Figure 3b). The VD
14 group was also more at risk for hemorrhage (RR=2.64, 95% CI= 1.05 to 6.63, p=0.04),^{2, 8, 10-12}
15 without evidence of statistical heterogeneity (Q-test , $p=0.94$, $I^2= 0\%$) (Figure 3c).

16 Episodes of RICH were only reported by one paper⁸, and thus did not lend themselves to a
17 pooled analysis. The RR was 0.41, with a 95% CI ranging from 0.24 to 0.70.

18 Risk of bias

19 The overall quality of the studies is poor (Appendix 4), with one underpowered RCT (N=122)
20 with high risk of bias with regard to blinding of trial personnel and of the outcome assessors.
21 Of the 5 observational studies, 2 were judged as serious risk of bias and the other 3 were
22 deemed at critical risk of bias according to the methodological assessment.

23 The risk of bias for the RCT was low on most domains, except blinding of study personnel,
24 which is inherently impossible given the nature of the intervention and the blinding of
25 clinicians to the intervention in the clinical phase. The retrospective observational cohorts
26 were judged as having overall serious⁹ and critical risk of bias respectively.^{2, 10, 11}

27 The criterion blinding could not be rated in the Cochrane tool since the monitoring device is
28 identifiable when placed.

29 **Discussion**

30 This is the first systematic review that describes the potential effects of VDs versus IP
31 monitor-guided management on patient outcomes. We found no difference in terms of
32 mortality or functional outcome between the two groups. IP monitors are associated with a
33 shorter ICU stay but not hospital stay and are associated with less complications, in particular
34 less infections. The risk of malfunction is comparable among devices. However, strong
35 inferences on effectiveness of VDs versus IP monitors cannot be made from this analyses
36 given the high risk of bias of the included studies.

1 The effect of ICP monitoring is the subject of an ongoing debate in the scientific literature.^{1,}
2 ¹³⁻¹⁵ General consensus remains that ICP monitoring is recommended in patients with severe
3 TBI who have traumatic abnormalities on the CT scan.¹⁶

4 Considerable practice variation exists with respect to the choice of monitoring device. A
5 recent questionnaire-based study carried out by our group in 66 centers in Europe¹⁶ showed
6 that both parenchymal and ventricular monitoring devices were available in more than half of
7 centers (59%). One-third of the participants indicated that they used only parenchymal
8 monitors, whereas one-tenth of the participants indicated that they used only ventricular
9 catheters.¹⁶

10 This variation noticed in the study carried out by our group can be explained in light of the
11 limited evidence base for clinical practice. When looking at studies that provide the best
12 quality evidence with a least risk of bias, the only RCT on the topic suggests the superiority of
13 monitoring and treatment using VDs⁸ for both mortality and functional outcome, potentially
14 also through a decrease in the number of patients requiring surgical decompression. Our meta-
15 analysis shows no difference between the two groups which likely arises from the pooling of
16 results with lower quality studies. Despite the importance of ICP monitoring and the clinical
17 relevance of the comparison between VDs and IP monitors, we only found 6 papers dealing
18 with this head-to-head comparison. This is perhaps due to the idea that a monitoring device in
19 itself cannot improve outcomes, but guide treatment and because certain imaging
20 characteristics (midline shift, mass lesions, narrow ventricles) might deter clinicians from
21 inserting VD, making RCTs difficult to carry out and less generalizable.

22 It is essential to distinguish acute craniotomy for the evacuation of life-threatening space-
23 occupying lesions from decompressive craniectomy, a rescue therapy to resolve intracranial
24 hypertension refractory to medical treatment because of the vastly different prognosis.
25 This was, however, only properly defined as such in the paper by Liu and colleagues.⁸ In the
26 other two papers that report this outcome^{9, 10}, it is unclear whether patients received a
27 decompressive craniectomy or a craniotomy with decompression of the lesion. Kasotakis et al
28 report “surgical decompression” and do not define it¹⁰, whereas Aiolfi et al report in the text
29 “The need for craniectomy” and “Craniotomy/Craniectomy performed within 24 hours” in the
30 table.⁹ When the results of Liu et al and Kasotakis et al were pooled, the difference was
31 significant in that the VD group required surgical decompression more often. When the
32 results of the Aiolfi study were added, the difference was no longer significant. Given the
33 major differences in prognosis between a craniotomy with evacuation of a lesion and a
34 craniectomy on patient outcomes, it is likely that confounding was introduced by adding the
35 Aiolfi study to the pooled results, owing in part to the large number of patients included.⁹
36 The overall complication rate and in particular to the risk of infection and haemorrhage were
37 higher for patients receiving a VD when compared to those receiving an IP monitor.

38 The infection risk for an VD in the literature ranges between as low as 0%¹⁷ and as high as
39 22%¹⁷, and this needs to be addressed when VDs are used by the implementation of a strict
40 protocol of insertion, care and maintenance. In this review the calculated infection rate and
41 overall complication rates were higher in the VD groups, ranging from 2%⁸ to 9%¹². The IP

1 monitor group had consistently very low prevalence of infection, usually under 1%.^{2, 10} It is
2 known that a longer duration of monitoring usually leads to a higher infection rate.¹² Only two
3 papers report the mean duration of monitoring and the pooled results show no statistically
4 significant difference between the two groups,^{8, 10} but future research on this topic needs to
5 address this potential confounder.

6 Despite the difference being non-significant in all of the individual studies, the aggregated
7 results show a significantly shorter duration of ICU admission in patients receiving IP
8 monitors. At first glance, it might appear that the lower complication rate leads to a shorter
9 ICU LOS. On average, patients spent one extra day in the ICU. Severe complications would
10 prolong ICU stay for longer than a day and the hospital LOS does not differ significantly.
11 This might, however, be a case of confounding by indication: the insertion of a ventricular
12 probe requires a patent ventricle, and is best accomplished when the ventricular system is not
13 displaced. In case of raised ICP the ventricles become slit and a considerable midline shift
14 may develop, making the surgical insertion of the probe difficult or impossible. There is the
15 risk, therefore, that VDs are used in less severe cases, where its insertion is feasible.

16 When looking at variables collected in the 6 included papers, we strikingly found no mention
17 of the effect of CSF drainage on therapy intensity level, save for the need for performing a
18 surgical decompression and the ICU LOS and number of episodes of RICH as indications of
19 therapy intensity (the latter only available in the RCT). We feel that this is a necessary
20 addition for future studies, as the beneficial effect of controlling ICP through CSF drainage
21 might be counteracted by the risk of adverse events. It is more likely to assume that VD use
22 decreases treatment intensity and is in this respect beneficial than to assume that it has, as a
23 standalone entity, a direct effect on patient outcomes.

24 Moreover, except for the only RCT on the topic by Liu and colleagues⁸, no other papers
25 report whether CSF was drained intermittently or continuously. Within the aforementioned
26 trial CSF was drained intermittently. So far only small studies suggest a potential benefit of
27 continuous drainage above intermittent.¹⁸ In addition, there was also no information available
28 of crossover patients, i.e. patients that received an VD after receiving an IP monitor and
29 whether there were differences in the readings. This also suggests another possible
30 confounder: the values indicated by VDs during drainage might provide inaccurately low
31 values, not detecting values above the threshold and leading to under-treatment.¹⁹
32 Furthermore, no mention was made in any of the papers whether antibiotic impregnated
33 catheters were used. These issues need to be dealt with when further research on this topic
34 will be carried out.

35 In light of the complications, the use of VDs might seem counterintuitive. However, in the
36 pediatric population continuous CSF drainage is a relatively common practice with evidence
37 to support improvements in both ICP management and injury biomarkers.²⁰ In the adult
38 population, however, only small studies show a potential benefit of continuous drainage¹⁸.
39 This statement also figures as a recommendation in the guidelines.¹

40 In light of many unanswered questions, a large comparative effectiveness study,²¹ such as the
41 ongoing CENTER-TBI and TRACK-TBI cohorts would be needed to address all of the

1 questions regarding the effectiveness, complication rate, and to assess the cost-effectiveness
2 of each device while keeping the risk of bias moderate or low and work around the
3 confounding. The topic of intermittent or continuous drainage also needs to be addressed in a
4 larger dedicated trial, and the focus should also be on the effect of CSF drainage on treatment
5 intensity.

6 Despite the fact that the only RCT on this topic shows better results for patient outcomes, it
7 did not create a paradigm shift in practice, nor does it figure in the current edition of the
8 guidelines¹. When all available data was pooled, the results of this RCT are challenged.
9 Further high-quality comparisons are needed to address this issue.

10 **Deviations from the protocol and limitations**

11 We were unable to access absolute values of the GOS(E) in order to dichotomize. The only
12 data available was the mean GOS for the two groups which is a limitation of this study. We
13 would have favored an ordinal approach to data analysis.

14 We also did not measure the relative risk of receiving an VD when one had received an IP
15 monitor first. We included some studies that did not respect our 85% severe TBI rule, but
16 given that we felt that the risk of infections when these devices are used in other injury types
17 or in mixed injury types are comparable, we avoided the introduction of confounding of our
18 results. VDs used in stroke are usually inserted in cases of intraventricular haemorrhage and
19 kept in until the blood clears, which might lead to a longer monitoring duration in the VD
20 group and consequently more infections. The pooled data available did not suggest a longer
21 monitoring duration with VDs, but only 2 of the 6 papers reported this outcome.

22 Subgroup analyses were impossible since the studies did not present the required data. Funnel
23 plots could also not be compiled as there were insufficient studies in order to do so.

24

25 **Conclusion**

26 This systematic review suggests that in patients with severe or moderate TBI the use of VDs
27 instead of IP monitors was not associated with less mortality or better functional outcome, but
28 the patients did suffer more complications. Overall, these results need to be interpreted with
29 caution given that the overall body of evidence is poor, consisting of mostly observational
30 studies with serious and critical risk of bias. There remains a need for high quality head-to-
31 head comparisons of VDs and IP monitors.

32

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36 **Conflict of interest**

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