Background

Conventional autologous bone graft has become the most widely used treatment for bone defects over time. Several factors contributed to its widespread application: it is easy to obtain, it combines osteogenic, osteoinductive and osteoconductive properties, it does not raise immune response or transmit infectious diseases [1, 2]. Furthermore, autologous bone graft can be harvested in a variety of forms and sizes from different donor sites [1, 2].

Selection of the autologous graft type in the treatment of bone defects has been mostly based on defect size: several authors do not recommend the use of the non-vascularized graft in defects larger than 5 cm [1–3]. The more technical demanding vascularized bone graft method is considered the best choice for larger size defects [2, 3]. However, in recent years, advances in graft harvesting technique [4] and in wound environment recovery using the polymethylmethacrylate (PMMA) induced membrane technique [5], renewed the interest in the use of the non-vascularized autologous bone graft. Infection also plays a role in graft selection and a 2-stage approach with delayed grafting is sometimes necessary [6].

The primary objective of this meta-analysis is to determine the bone union rate of post-traumatic bone defects treated with the different autologous bone graft techniques. The secondary objective is to determine the rate of infection after this treatment.
Methods

Data collection and extraction

Prior to doing the electronic search, a written protocol was established according to guidelines for systematic reviews (AMSTAR, MOOSE and PRISMA) [7–9]. An electronic search was conducted in Medline restricted to English language, to human species, and to a publication period from January 1999 to November 2014. The search terms and Boolean operators used were: ‘fracture’ AND (‘bone loss’ OR ‘defect’ OR ‘defects’) AND ‘bone graft’. Additionally an electronic search was done in the Cochrane Library with the terms: fracture AND bone loss AND defect OR defects AND bone graft.

Two reviewers (MA, AA) independently scrutinized the list of titles of all the retrieved citations and, if necessary, the abstracts to determine usefulness of the article. The final selection was based on the full text version of the potentially relevant articles that were assessed independently by the reviewers. All references cited in these selected studies were manually searched along with the “related articles” searches in PubMed engine for additional relevant studies. Papers published by the same research group and studying the same factors were checked for duplicate data. Where duplication occurred the less detailed paper was discarded.

We included only original reports that presented the results of at least ten cases of bone defects secondary to open fractures, post-traumatic nonunion or infected bone resection. The exclusion criteria were: bone defects after tumor resection; bone defects after reduction and fixation of closed metaphyseal fracture of long bones; studies with more than 25 % of the defect not located in long bones (forearm, humerus, femur or tibia); studies with more than 25 % of the defects treated with osteo-conductive biomaterials in addition to the bone graft; cases with the use of osteoinductive factors in the graft; studies mostly about bone defects in children and studies that did not report the information about healing after treatment. When the information of each patient in a study was presented in the text and/or tables, cases that met the exclusion criteria were removed and the remaining patients were enrolled in the analysis.

Included studies were classified according the Oxford Centre for Evidence-Based Medicine system and a modified version of the Coleman methodology score [10] (Additional file 1). Data was extracted by one of the reviewers and then checked by the second. Disagreements were solved via discussion and consensus between the two reviewers. The following definitions were used for data extraction: primary union described as bone union achieved after bone grafting, secondary union as bone union achieved with a further surgery after the bone graft. Of note, a graft fracture was considered a union related complication only when the original study classified it in this manner, and cases with union before lost of follow up were considered as treated. Treatment failures were viewed as the loss of the graft in the postoperative period that required debridement and a new graft, the absence of bone union during follow-up or a new bone defect treatment (bone transport, amputation, etc.). Preoperative infection refers to the presence of infection (active or quiescent) or absence of it when bone defect treatment was implemented. Postoperative infection was infection reported as a complication after bone graft procedure. We considered that PMMA was used as an adjuvant in bone defect treatment (induced membrane technique) only when authors reported its use for this purpose.

Assessment of publication bias

Susceptibility of the systematic review to publication bias was formally assessed with the Egger test [11].

Quantitative data synthesis

To stabilize variance, the bone union proportions were subject to a Freeman-Tukey arcsine square root transformation and back-transformed according to Miller after quantitative data synthesis [12, 13]. With the normalized data, heterogeneity was assessed using both Cochrane’s Q test and the inconsistency measure I² suggested by Higgins [14]. A cut-off of P < 0.10 was used to indicate heterogeneity. Values of I² equal to 25 %, 50 % and 75 % denoted a low, moderate and high degree of statistical heterogeneity. As data from a series of studies that had been performed independently are thought to be not functionally equivalent, a random effects model approach was used to combine estimates. Confidence intervals within studies were achieved using the exact binomial method. To perform a sub-group analysis, the studies were divided according to graft vascularization in two major categories: non-vascularized bone graft or vascularized bone graft. Analyses were performed using STATA (version 13.0) and Comprehensive Meta-analysis (version 2.0).

Results

Selection of studies

The Medline search resulted in 338 citations and after the abstract review 21 were considered as potentially eligible and all of them had the full version reviewed. References of these articles were manually screened and also the related citations tool resulting in further 38 potentially eligible articles, totaling 59 papers to review. The Cochrane Library search did not result in additional studies. After the full version review, 34 studies met the inclusion/exclusion criteria (Fig. 1) (Additional file 2). In seven of the 34 studies some cases were excluded from the analysis (Additional file 3). A total of 749
patients with 750 bone defects were included in this meta-analysis.
Concerning study characteristics, one was a randomized controlled trial, one was a prospective case series, three were retrospective comparative case series and 29 were retrospective case series (Table 1). Only Pelissier et al. [15] was a comparison between vascularized and non-vascularized bone graft. The studies achieved 37.1 points (21 to 72) out of 100 in the quality assessment tool. The inter rater agreement in regards to the quality assessment between the reviewers was considerably high (ICC = 0.78; 95 % CI 0.75 to 0.94).

Publication bias
The shape of the funnel plot revealed evidence of asymmetry for both primary and secondary union (Fig. 2). The Egger’s test showed evidence of publication bias ($p < 0.001$ for primary union and $p < 0.001$ for secondary union).

Bone union rate
Primary bone union was documented in 33 studies [15–47] ($Q = 87.53$, $df = 32$, $P < 0.001$; $I^2 = 63.4$ %) and secondary bone union was documented in 34 studies [15–48] ($Q = 38.65$, $df = 33$, $P = 0.23$; $I^2 = 14.6$ %). Union rates as primary ranged between 48 % and 100 % across eligible studies. Using random-effects weights, the summary (pooled) union rate was 91 % (95 % CI: 87–95 %). Union rates as secondary ranged between 81 % and 100 % across eligible studies. Using random-effects weights, the summary (pooled) union rate was 98 % (95 % CI 96–99 %).

For comparison of vascularized versus non-vascularized graft the study from Toh et al. [18] and the study from Muramatsu et al. [20] were omitted as they used a mixed technique. The study of Pelissier et al. [15] included patients treated either with vascularized or non-vascularized graft, thus this publication contributed to both groups in the sub-group analysis (Table 2).

When analyzing the primary bone union, significant intra-group heterogeneity was observed (Vascularized: $Q = 37.07$, $df = 18$, $P < 0.01$; $I^2 = 51.4$ %; Non-vascularized: $Q = 47.48$, $df = 12$, $P < 0.001$; $I^2 = 74.7$ %). However, there was no statistical difference between the two groups ($P = 0.372$) supporting the pooling of all studies into one pooled measure. Using random-effects weights, the summary (pooled) union rate was 93 % (95 % CI: 89–97 %) for the vascularized group and 89 % (95 % CI: 79–97 %) for the non-vascularized group (Fig. 3a).
Meta-regression was performed to investigate potential sources of heterogeneity within study for primary bone union. The main factor investigated was bone defect size additionally adjusted for age and proportion of female patients. Both univariable and multivariable meta-regression did not show any association of union rate and bone defect size (Univariable: vascularized: \( P = 0.677 \); non-vascularized: 0.202. Multivariable: vascularized: \( P = 0.381 \); non-vascularized: \( P = 0.226 \)).

When analyzing the secondary bone union, no significant intra-group heterogeneity was observed (Vascularized: \( Q = 18.22, df = 19, P = 0.508; I^2 = 0.0 \% \); Non-vascularized: \( Q = 15.20, df = 12, P = 0.231; I^2 = 21.0 \% \)), neither difference between groups was noted (\( P = 0.106 \)). Using random-effects weights, the summary (pooled) secondary union rate was 98 % (95 % CI: 97–100 %) for the vascularized group and 96 % (95 % CI: 91–99 %) for the non-vascularized group.

### Table 1: Studies and cases descriptive characteristics

| Authors         | Year    | Treatment period | Study type | LE (n) | Age (y) [range] | Male/female | Bone defect location (femur/tibia/humerus/forearm/other bones) | FU (mts) |
|-----------------|---------|------------------|------------|--------|----------------|-------------|-------------------------------------------------------------|----------|
| Ring et al.     | 2000    | nr               | R-CS IV    | 15     | 48 [22 - 80]   | 9/6         | -/-/-/-/-        | 31       |
| Tu et al.       | 2001    | 1990–1993        | R-CS IV    | 48     | 48 [15 - 62]   | 40/8        | -/10/32/2/4/-    | 72       |
| Toh et al.      | 2001    | 1983–1998        | R-CS IV    | 19     | 53 [21 - 84]   | 17/2        | -/-/-/-/-        | 98       |
| Heitmann et al. | 2002    | nr               | R-CS IV    | 12     | 43 [16 - 79]   | 7/5         | -/-/-/-/-        | tn       |
| Muramatsu et al.| 2003    | 1985–2000        | R-CS IV    | 13     | 51 [27 - 80]   | 6/7         | -/-/-/-/-        | tn       |
| Pelissier et al.| 2003    | 1984–1999        | R(C)-CS IV | 40     | tn             | tn          | tn               | tn       |
| Yajima et al.   | 2004    | 1976–2000        | R-CS IV    | 20     | 37 [17 - 73]   | 16/4        | -/9/8/-/-/1/1    | 64       |
| Lee et al.      | 2004    | 1982–2001        | R-CS IV    | 51     | 41 [15 - 66]   | 48/3        | -/-/-/-/-/-      | non      |
| Adani et al.    | 2004    | 1993–2000        | R-CS IV    | 11     | 38 [16 - 65]   | 5/6         | -/-/-/-/-/-      | tn       |
| Ring et al.     | 2004    | 1983–2001        | R-CS IV    | 35     | 40 [21 - 66]   | 18/7        | -/-/-/-/-/-      | 43       |
| Yazar et al.    | 2004    | 1993–2000        | R-CS IV    | 61     | 37.5 [10 - 82] | 42/19       | 7/49/-/-/-/6     | 58       |
| Safoury         | 2005    | nr               | R-CS IV    | 18     | 34 [22 - 46]   | 16/2        | -/-/-/-/-/-      | 36       |
| Jones et al.    | 2006    | 2000–2003        | R-CS IV    | 15     | 38 [18 - 71]   | 13/2        | -/-/-/-/-/-      | tn       |
| El-Sayed et al. | 2007    | nr               | R-CS IV    | 12     | 25 [12 - 40]   | 11/1        | -/-/-/-/-/-      | 24       |
| Ristiniemi et al.| 2007    | 2000–2004        | R-CS IV    | 23     | 35 [14 - 75]   | 16/7        | -/-/-/-/-/-      | non      |
| Adani et al.    | 2008    | 1994–2004        | R-CS IV    | 13     | 37 [21 - 62]   | 10/3        | -/-/-/-/-/-      | non      |
| El-Gammal et al.| 2008    | 1995–2004        | R(C)-CS IV | 13     | 31.5 [nr]     | 11/2        | -/-/-/-/-/-      | 38       |
| Ryzewicz et al. | 2009    | 1998–2007        | R(C)-CS IV | 18     | 34.2 [18 - 51] | 11/7        | -/-/-/-/-/-      | non      |
| Allende et al.  | 2009    | 1996–2008        | R-CS IV    | 10     | 32.8 [11 - 56] | 9/1         | -/-/-/-/-/-      | non      |
| Cavadas et al.  | 2010    | 2000–2008        | R-CS IV    | 41     | 38 [17 - 64]   | 39/2        | -/-/-/-/-/-      | non      |
| McCall et al.   | 2010    | 2003–2007        | P-CS IV    | 21     | 30.6 [nr]     | 13/8        | -/-/-/-/-/-      | non      |
| Sun et al.      | 2010    | 2005–2007        | R-CS IV    | 10     | 31 [16 - 50]   | 9/1         | -/-/-/-/-/-      | 26       |
| Aparid et al.   | 2010    | nr               | R-CS IV    | 12     | 40.6 [18 - 74] | 10/2        | -/-/-/-/-/-      | 39       |
| Zhen et al.     | 2010    | 2000–2007        | R-CS IV    | 28     | 31.5 [17 - 56] | 21/7        | -/-/-/-/-/-      | 36       |
| Chai et al.     | 2010    | 2005–2007        | R-CS IV    | 16     | 31 [16 - 50]   | 10/6        | -/-/-/-/-/-      | 18       |
| Georgescu et al.| 2011    | 1997–2007        | R-CS IV    | 44     | 30.5 [5 - 66]  | 33/11       | 3/2/2/3/3/11     | 23       |
| Chung et al.    | 2011    | 1989–2007        | R-CS IV    | 10     | 25.3 [16 - 43] | 8/2         | -/-/-/-/-/-      | 41       |
| Niu et al.      | 2011    | 2003–2008        | R-CS IV    | 19     | 38.9 [18 - 61] | 12/7        | 8/-/-/-/-/-      | 39       |
| Liang et al.    | 2012    | 1996–2006        | R-CS IV    | 16     | 33.3 [21 - 46] | nr 16/6/6/6/6/6 | 39       |
| Gulan et al.    | 2012    | 1991–1998        | R-CS IV    | 10     | 30 [22 - 51]   | 10/0        | -/-/-/-/-/-      | 144      |
| Liang et al.    | 2012    | 2001–2007        | R-CS IV    | 14     | 34.3 [23 - 48] | 11/3        | -/-/-/-/-/-      | 67       |
| Gao et al.      | 2012    | 2004–2006        | R-CS IV    | 18     | 34 [16 - 56]   | 13/5        | -/-/-/-/-/-      | 40       |
| Niu et al.      | 2012    | 1993–2008        | R-CS IV    | 22     | 33.8 [17 - 60] | 14/8        | -/-/-/-/-/-      | 39       |
| Özaksar et al.  | 2012    | 2003–2009        | R-CS IV    | 21     | 32 [16 - 47]   | 19/2        | -/-/-/-/-/-      | 74       |

LE level of evidence, n number of patients included in this review, y years, mts months, FU follow-up, R retrospective, P prospective, CS case series, C controlled, RCT randomized controlled trial, nr not reported, tn technical note (see Additional file 3)
Infection pre and post-treatment

Infection status of the cases was reported pre- and post-operative in 22 studies [16, 18, 19, 21, 23, 24, 26, 27, 29–33, 35, 36, 40, 41, 43–47]. The pooled estimate of mean effect size showed about 6-fold decrease of infection after treatment compared with pre-operative situation (OR = 0.17 (95% CI 0.08 to 0.36), p < 0.001; Q = 58.6, p < 0.001, df = 21, I² = 64.2 %). Therefore, a subgroup analysis was performed. A significant decrease of post-treatment infection was observed among the vascularized graft group (n = 12; OR = 0.08 (95% CI 0.03 to 0.23), p < 0.001) but not in the non-vascularized group (n = 10; OR = 0.43 (95% CI 0.15 to 1.22), p = 0.114). Moreover, a statistical difference between the two groups was found (Q = 4.350; P = 0.037) (Fig. 4).

As heterogeneity in the subgroup analysis may be due to the presence of outlying studies, a sensitivity analysis was conducted excluding the studies that presented the highest OR (Jones et al. [27], Ristiniemi et al. [29] and Niu et al. [41]). After these studies were excluded a moderate degree of heterogeneity (I² = 63.7 %) was found. In the sensitivity analysis there was no statistical difference between the two techniques (Q = 1.146; P = 0.284) and the non-vascularized group also showed a statistically significant decrease of post-operative infection (n = 7; OR = 0.207 (95% CI 0.06–0.77)).

Additionally, investigation of heterogeneity was performed by means of meta-regression including age, percentage of females and months of delay from injury to treatment. No variables showed a significant association with the risk of post-treatment infection.

Discussion

Bone union

The primary bone union rate expected for the bone graft techniques is 91%. In some circumstances, additional procedures such as the change of a broken implant, compression in the nonunion site or cancellous graft in nonunion areas at bone ends, may be necessary and they raised the union rate to 98% in published studies (Additional file 4) [15, 17–23, 25–31, 33–35, 39, 41, 42, 46–48].

Defect size as a guide to select graft

Only few studies presented a description of the method used to define and measure the bone defect [27, 29, 31, 46]. Small defects that might have been susceptible to spontaneous regeneration were present in some studies. They were treated not only with non-vascularized graft but also with vascularized bone graft.

Studies about vascularized bone grafts have been performed on larger bone defects but association of union rate and bone defect size wasn’t found between the vascularized and non-vascularized grafts. Limitations of this conclusion include also a potential selection bias: some recent studies about non-vascularized graft were excluded because of the addition of growth factor or biomaterial to the graft. Despite the limitation of this study, our data suggests that selection of graft technique shall not be guided only by defect size. Patient expectations, surgeon experience, soft tissue condition and a trained staff to perform microsurgery are elements that must be carefully judged before making a decision on the graft to be used.
Infection pre-post-treatment

The pooled estimate of mean effect size showed a decrease of infection after treatment compared with the pre-operative situation. However, these findings should be interpreted with caution due to the presence of a moderate degree of statistical heterogeneity. According to Table 2, the healing rate per treatment varied across different graft types and donor areas.

### Table 2: Graft type and healing rate per treatment

| Authors             | n  | BD Mean (cm) | Treatment type          | Donor area/associated technique | Primary union | Secondary union |
|---------------------|----|--------------|-------------------------|---------------------------------|---------------|-----------------|
| Ring et al. [16]    | 15 | 3 [2–6]      | ICBG                    | ICBG (15)                       | 93 %          | 93 %            |
| Pelissier et al. [15]| 16 | 4.3 [nt]     | ICBG                    | ICBG (16)                       | 75 %          | 81 %            |
| Jones et al. [27]   | 15 | 4 [2.5–7]    | ICBG                    | ICBG (15)                       | 67 %          | 93 %            |
| Ryzewicz et al. [31]| 18 | 3.8 [2–6]    | ICBG                    | ICBG (18)                       | 89 %          | 94 %            |
| Niu et al. [46]     | 22 | tn [tn]      | ICBG                    | ICBG (22)                       | 95 %          | 100 %           |
| Gulan et al. [43]   | 10 | 4 [2–7]      | ICBG                    | ICBG (10)                       | 100 %         | 100 %           |
| Ring et al. [24]    | 35 | 2.2 [1–6]    | Multiple DS             | ICBG (33)/Ulna (4)              | 100 %         | 100 %           |
| El-Sayed et al. [28]| 12 | 7 [6–10]     | Multiple DS             | ICBG (8)/Fibula (12)            | 92 %          | 92 %            |
| Niu et al. [41]     | 19 | nr [nr]      | Multiple DS             | ICBG (19)/Fibula (2)            | 95 %          | 95 %            |
| Ristiniemi et al. [29]| 23 | 5.2 [3.5–10] | ICBG + biomembrane      | ICBG (23)/biomembrane (23)      | 61 %          | 96 %            |
| Allende et al. [32] | 10 | 3.2 [1–7]    | ICBG + biomembrane      | ICBG (10)/biomembrane (10)      | 100 %         | 100 %           |
| Apari et al. [36]   | 12 | 8.7 [6–15]   | ICBG + biomembrane      | ICBG (12)/TCF (4)/biomembrane (12)| 92 %          | 92 %            |
| McColl et al. [34]  | 21 | 6.6 [2–14.5] | RIA + biomembrane       | RIA (21)/biomembrane (18)       | 48 %          | 81 %            |
| Heitmann et al. [19]| 12 | 9.2 [8–12]   | Free one DS             | Fibula (12)                     | 75 %          | 92 %            |
| Lee et al. [22]     | 51 | 10.5 [4.5–17]| Free one DS             | Fibula (51)                     | 92 %          | 98 %            |
| Adani et al. [23]   | 11 | 8.7 [6–13]   | Free one DS             | Fibula (11)                     | 73 %          | 82 %            |
| Safoury [26]        | 18 | nr [nr]      | Free one DS             | Fibula (18)                     | 94 %          | 100 %           |
| Adani et al. [30]   | 13 | 10.5 [6–16]  | Free one DS             | Fibula (13)                     | 69 %          | 92 %            |
| El-Gammal et al. [48]| 13 | 12.6 [nr]    | Free one DS             | Fibula (13)                     | nr            | 100 %           |
| Sun et al. [35]     | 10 | 9.5 [6–17]   | Free one DS             | Fibula (10)                     | 90 %          | 100 %           |
| Zhen et al. [37]    | 28 | nr [9–17]    | Free one DS             | Fibula (28)                     | 100 %         | 100 %           |
| Chai et al. [38]    | 16 | 13.8 [5–20]  | Free one DS             | Fibula (16)                     | 100 %         | 100 %           |
| Liang et al. [44]   | 14 | 6.9 [5–9]    | Free one DS             | Fibula (14)                     | 100 %         | 100 %           |
| Liang et al. [42]   | 16 | 16.4 [14–20] | Free one DS             | Fibula (16)                     | 94 %          | 100 %           |
| Gao et al. [45]     | 18 | 9.2 [7–14]   | Free one DS             | Fibula (18)                     | 100 %         | 100 %           |
| Özaksar et al. [47] | 21 | 10 [6–18]    | Free one DS             | Fibula (21)                     | 81 %          | 95 %            |
| Toh et al. [18]     | 19 | 4.9 [1–11]   | Pedicle one DS          | Fibula (19)                     | 95 %          | 100 %           |
| Chung et al. [40]   | 10 | 5.4 [4–8]    | Pedicled one DS         | Fibula (10)                     | 100 %         | 100 %           |
| Yajima et al. [21]  | 20 | 9.6 [3–24]   | Free + pedicle one DS   | Free fibula (16)/pedicle fibula (4)| 85 %          | 90 %            |
| Georgescu et al. [39]| 44 | 8.2 [4–14]   | Free one DS             | Free rib (44)                   | 98 %          | 98 %            |
| Pelissier et al. [15]| 24 | 9.8 [nr]     | Free multiple DS        | Fibula (12)/iliac (10)/arm (2)  | 88 %          | 88 %            |
| Yazar et al. [25]   | 62 | 11.7 [6–18]  | Free multiple DS        | Fibula (50)/iliac (6)/rib (6)   | 87 %          | 95 %            |
| Cavadas et al. [33] | 41 | nr [4–17]    | Free multiple DS + biomembrane | Fibula (38)/iliac (3)/biomembrane (32)| 98 %          | 100 %           |
| Muramatsu et al. [20]| 13 | 1.8 [1–4]    | Free multiple DS + ICBG | Fibula (8)/femur (4)/scapula (1)/ICBG (8)| 85 %          | 100 %           |
| Tu et al. [17]      | 48 | 10.2 [6.5–19]| Free multiple DS + ICBG | Fibula (41)/iliac (4)/Rib (3)/ICBG (48)| 94 %          | 100 %           |

n number of bone defects, ICBG iliac crest bone graft, DS graft donor site, TCF tricalcium phosphate, nr technical note (see Additional file 3)
Fig. 3 Forest plot of bone union (% of union rates) in patients with vascularized and non-vascularized bone graft (random effects model). 

**a** Primary union

**b** Secondary union
to the results of this meta-analysis, vascularized graft showed a significant decrease of post-treatment infection. Again, this conclusion is limited. Infection definition varies between the included studies and several different surgical techniques were used. Although we cannot give evidence to support this recommendation, most of the studies suggest a two-step reconstruction as the standard approach to manage infected bone defects: an extensive debridement, followed by antibiotic treatment before graft surgery [16, 21, 26, 29, 31, 32, 36, 40, 43, 44]. Furthermore, some of the studies use PMMA as a local antibiotic de-liverya and/or due to its ability to induce a biological membrane at the defect site [21, 29, 32–34, 36].

Quality of the evidence
The overall quality of the included studies is poor. Most of them are non-randomized observational studies with serious limitations. There was evidence of publication bias for primary and secondary bone union, with higher union rates in bigger studies. Overall sample size allows obtaining several statistically significant results. However, the level of evidence of these findings is low or very low due to the heterogeneity of the pooled data and the risk of bias caused by the studies’ design.

Overall completeness and applicability of evidence
The included studies provide the most complete information available concerning union rates after autologous graft for bone defects; however, different factors may have added to the heterogeneity of the pooled results, such as different surgical steps and different sample sizes reflecting different levels of experience, incomplete information about complications. Additionally, information regarding surgical steps was limited in several studies. Finally, data concerning potential confounding factors, such as patients selection criteria, soft tissue treatment and definition of complications were also incomplete.
Additional files

Additional file 1: Table modified Coleman methodology score for bone defect. (DOXC 74 kb)
Additional file 2: Table studies excluded after full text review. (DOXC 99 kb)
Additional file 3: Table removed cases from included studies and technical notes. Technical notes represent values related to the entire sample of the studies where it was not possible to individualize data of the included cases. (DOXC 52 kb)
Additional file 4: Table additional procedures to achieve healing. (DOXC 60 kb)

Abbreviation
PMMA: Polymethylmethacrylate

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Availability of data and materials
Data was presented in the main text and in the additional files. It is also available from published papers as per references.

Authors' contributions
MA and AA made substantial contributions to: conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript and its critical revision. MA and AM made substantial contributions to: drafting of manuscript and its critical revision. MA made substantial contributions to: conception and design, interpretation of data, drafting of manuscript and its critical revision. All of the authors reviewed and approved the final version.

Competing interests
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Consent for publication
Not applicable.

Ethics approval and consent to participate
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